CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761398Orig1s000
761398Orig2s000

OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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:	March 21, 2025
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	BLA 761398
Product Name, Dosage Form, and Strength:	Conexxence (denosumab-bnht) injection, 60 mg/mL
Applicant Name:	Fresenius Kabi USA, LLC
FDA Received Date:	March 19, 2025
TTT ID #:	2024-8850-2
DMEPA 1 Safety Evaluator:	Amy J. Bao, PharmD, MPH
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 PURPOSE OF MEMORANDUM

Fresenius Kabi USA, LLC submitted revised container labels and carton labeling received on March 19, 2025 for Conexxence. The Division of General Endocrinology (DGE) requested that we review the revised container labels and carton labeling for Conexxence (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

Fresenius Kabi USA, LLC implemented all of our recommendations and we have no additional recommendations at this time.

[a] Bao, A. Review of Revised Label and Labeling for Conexxence (BLA 761398). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2025 Feb 27. TTT ID: 2024-8850-1.

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/s/

AMY J BAO
03/21/2025 10:10:23 AM

YEVGENIYA M KOGAN
03/24/2025 11:03:43 AM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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:	March 21, 2025
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	BLA 761398
Product Name, Dosage Form, and Strength:	Bomyntra (denosumab-bnht) injection, 120 mg/1.7 mL (70 mg/mL)
Applicant Name:	Fresenius Kabi USA, LLC
FDA Received Date:	March 19, 2025
TTT ID #:	2024-8851-2
DMEPA 1 Safety Evaluator:	Amy J. Bao, PharmD, MPH
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 PURPOSE OF MEMORANDUM

Fresenius Kabi USA, LLC submitted revised container labels and carton labeling received on March 19, 2025 for Bomyntra. The Division of General Endocrinology (DGE) requested that we review the revised container labels and carton labeling for Bomyntra (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

Fresenius Kabi USA, LLC implemented all of our recommendations and we have no additional recommendations at this time.

[a] Bao, A. Review of Revised Label and Labeling for Bomyntra (BLA 761398). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2025 Feb 27. TTT ID: 2024-8851-1.

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AMY J BAO
03/21/2025 10:12:06 AM

YEVGENIYA M KOGAN
03/24/2025 11:04:06 AM

Memorandum to File

Date	March 24, 2025
Application Type	BLA
Application Number(s)	761398
Proper Name	denosumab-bnht
Trade Name	Bomyntra
Product Code	FKS518
Applicant	Fresenius Kabi USA, LLC

Fresenius Kabi USA, LLC submitted a 351(k) BLA seeking licensure of FKS518 as proposed interchangeable biosimilars to Prolia and Xgeva (denosumab).

It is standard clinical practice for Xgeva to be given by a healthcare provider. In clinical trials of Xgeva, the product was administered in a healthcare setting. Most commonly, Xgeva is given as part of a cancer care regimen in an infusion center where patients' electrolytes can be repleted and hypersensitivity reactions can be monitored. The labeling for Xgeva includes a Warning and Precaution stating that "[c]linically significant hypersensitivity including anaphylaxis has been reported with use of Xgeva. Reactions may include hypotension, dyspnea, upper airway edema, lip swelling, rash, pruritus, and urticaria. If an anaphylactic or other clinically significant allergic reaction occurs, initiate appropriate therapy and discontinue Xgeva therapy permanently."

If a patient were to receive Xgeva or one of its biosimilars from a pharmacy and self-administer it, there would be concern that the patient's calcium and phosphorus may be low without appropriate repletion at the time of administration, and the patient would not be monitored for potential hypersensitivity reactions.

The most recently approved Xgeva labeling does not include a statement that Xgeva should be administered by a healthcare provider. On February 11, 2025, the FDA issued a Prior Approval Supplemental request letter to Amgen requesting it submit a PAS to add a statement in the Xgeva labeling that the product should be administered by a healthcare provider.

The concerns relating to self-administration of Xgeva described above also apply to Fresenius Kabi's proposed interchangeable biosimilar to Xgeva. Therefore, the approved labeling for that product (with a conditionally approved proprietary name "Bomyntra") will include a statement that the product should be administered by a health care provider in Section 2.1 of the Prescribing Information and on its carton.

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/s/

CHRISTY L OSGOOD
03/24/2025 02:23:44 PM

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

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

Memorandum

Date: March 7, 2025

To: Julie Van der Waag, Director, Project Management Staff
Division of General Endocrinology Products (DGE)

LaiMing Lee, PhD, Associate Director for Labeling, DGE

From: Jeena Sun, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Emily Dvorsky, PharmD, Team Leader, OPDP

Subject: OPDP Labeling Comments for BOMYNTRA (denosumab-bnht) injection, for subcutaneous use

BLA: 761398

Background:
In response to DGE's consult request dated May 3, 2024, OPDP has reviewed the proposed Prescribing Information (PI) and carton and container labeling for the original BLA submission for BOMYNTRA (denosumab-bnht) injection, for subcutaneous use, proposed biosimilar to US-licensed XGEVA (denosumab) under BLA 125320.

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

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 February 10, 2025, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Jeena Sun at (301) 796-9699 or Jeena.Sun@fda.hhs.gov.

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/s/

JEENA L SUN
03/07/2025 02:47:20 PM

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:	March 5, 2025
To:	Julie Van der Waag, MPH Director, Project Management Staff **Division of General Endocrinology (DGE)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Lonice Carter, MS, RN, CNL, NHDP-BC Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Meena Savani, PharmD Regulatory Reviewer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (nonproprietary name):	FKS518 (denosumab-bnht)[1]
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	BLA 761398
Applicant:	Fresenius Kabi USA, LLC

[1] FKS518 has been developed as a proposed interchangeable biosimilar with US-licensed Prolia (denosumab). The proposed proprietary name, Conexxence, was found conditionally acceptable on June 18, 2024. The nonproprietary name, denosumab-bnht, was found conditionally acceptable on December 23, 2024.

1 INTRODUCTION

On March 25, 2024, Fresenius Kabi USA, LLC submitted for the Agency's review an original Biologics License Application (BLA) 761398 FKS518 (denosumab-bnht) injection, for subcutaneous use. This BLA proposes FKS518 (denosumab-bnht) as an interchangeable biosimilar with US-licensed Prolia (denosumab).

The Applicant proposes the same indications as US-licensed Prolia (denosumab), which are as follows:

- Treatment of Postmenopausal Women with Osteoporosis at High Risk for Fracture
- Treatment to Increase Bone Mass in Men with Osteoporosis
- Treatment of Glucocorticoid-Induced Osteoporosis
- Treatment of Bone Loss in Men Receiving Androgen Deprivation Therapy for Prostate Cancer
- Treatment of Bone Loss in Women Receiving Adjuvant Aromatase Inhibitor Therapy for Breast Cancer

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 General Endocrinology (DGE) on May 3, 2024, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for FKS518 (denosumab-bnht) injection, for subcutaneous use.

The Risk Evaluation and Mitigation Strategy (REMS) is being reviewed by the Division of Mitigation Assessment and Medication Errors Surveillance (DMAMES) and will be provided to DGE under separate cover.

2 MATERIAL REVIEWED

- Draft FKS518 (denosumab-bnht) MG received on March 25, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 28, 2025.
- Draft FKS518 (denosumab-bnht) Prescribing Information (PI) received on March 25, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 28, 2025.
- Approved Prolia (denosumab) injection, for subcutaneous use comparator labeling dated March 5, 2024.

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 MG 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 MG document using size 10 font.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- evaluated the MG per the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable

4 CONCLUSIONS

The MG 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 MG 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 MG.

Please let us know if you have any questions.

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/s/

MARY E CARROLL
03/05/2025 08:41:58 AM

MEENA R SAVANI
03/05/2025 09:39:04 AM

MARCIA B WILLIAMS
03/05/2025 11:53:54 AM

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

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

Memorandum

Date: March 4, 2025

To: Julie Van der Waag, Director, Project Management Staff
Division of General Endocrinology Products (DGE)

LaiMing Lee, Associate Director for Labeling (DGE)

From: Meena Savani, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sapna Shah, Team Leader, OPDP

Subject: OPDP Labeling Comments for CONEXXENCE (denosumab-bnht) injection, for subcutaneous use

BLA: 761398

Background:
In response to DGE's consult request dated May 3, 2024, OPDP has reviewed the proposed Prescribing Information (PI) and Medication Guide for the BLA for CONEXXENCE (denosumab-bnht) injection, for subcutaneous use (CONEXXENCE), proposed biosimilar to US-licensed PROLIA (denosumab) (BLA 125320).

PI and Medication Guide:
OPDP's review of the proposed CONEXXENCE PI is based on the draft labeling e-mailed to OPDP on February 28, 2025, and we have no comments at this time.

A combined OPDP and Division of Medical Policy Programs (DMPP) review for the CONEXXENCE Medication Guide 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 to the electronic document room on February 10, 2025, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Meena Savani at 240-402-1348 or Meena.Savani@fda.hhs.gov.

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/s/

MEENA R SAVANI
03/04/2025 01:37:55 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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

Date of This Review:	February 27, 2025
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	BLA 761398
Product Name, Dosage Form, and Strength:	Conexxence (denosumab-bnht) injection, 60 mg/mL
Applicant Name:	Fresenius Kabi USA, LLC
FDA Received Date:	February 10, 2025
TTT ID #:	2024-8850-1
DMEPA 1 Safety Evaluator:	Amy J. Bao, PharmD, MPH
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 PURPOSE OF MEMORANDUM

Fresenius Kabi USA, LLC submitted revised container labels and carton labeling received on February 10, 2025 for Conexxence. The Division of General Endocrinology (DGE) requested that we review the revised container labels and carton labeling for Conexxence (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 container labels 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, below.

3 RECOMMENDATIONS FOR FRESENIUS KABI USA, LLC

A. Container Labels

1. As currently presented, the branded container label does not include the assigned NDC number at the top of the principal display panel. We request that you include the NDC number or placeholder on the principal display panel of the container label per 21 CFR 201.2.

B. Carton Labeling

1. The nonproprietary name is not at least half the size of the proprietary name on the principal display panel and side panel of the branded carton labeling. We refer you to 21 CFR 201.10(g)(2) which states that the nonproprietary name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features. Revise the nonproprietary name to be in accordance with 21 CFR 201.10(g)(2).
2. For consistency with Section 2.3 of the Prescribing Information, please revise the statement [redacted (b) (4)] to "Conexxence should be administered by a healthcare provider" or "Denosumab-bnht should be administered by a healthcare provider" (for unbranded labeling).
3. We note the room temperature storage duration indicated on the side panel has been changed from [redacted (b) (4)] to "up to 14 days". Please revise the storage information on the branded and unbranded carton labeling to align with the storage information in the Prescribing Information.

[a] Bao, A. Label and Labeling Review for Conexxence (BLA 761398). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2025 Jan 30. TTT ID: 2024-8850.

4. We note the "PC" placeholder on the human-readable product information of the unbranded carton labeling has been changed to an NDC number, while the branded carton labeling still has a "PC" placeholder. Please confirm if this change is intentional and/or make revisions if needed.

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/s/

AMY J BAO
02/27/2025 01:53:51 PM

YEVGENIYA M KOGAN
02/28/2025 01:42:39 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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

Date of This Review:	February 27, 2025
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	BLA 761398
Product Name, Dosage Form, and Strength:	Bomyntra (denosumab-bnht) injection, 120 mg/1.7 mL (70 mg/mL)
Applicant Name:	Fresenius Kabi USA, LLC
FDA Received Date:	February 10, 2025
TTT ID #:	2024-8851-1
DMEPA 1 Safety Evaluator:	Amy J. Bao, PharmD, MPH
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 PURPOSE OF MEMORANDUM

Fresenius Kabi USA, LLC submitted revised container labels and carton labeling received on February 10, 2025 for Bomyntra. The Division of General Endocrinology (DGE) requested that we review the revised container labels and carton labeling for Bomyntra (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 container labels 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, below.

3 RECOMMENDATIONS FOR FRESENIUS KABI USA, LLC

A. Container Labels (Prefilled Syringe and Vial)

1. As currently presented, the branded container labels do not include the assigned NDC number at the top of the principal display panel. We request that you include the NDC number or placeholder on the principal display panel of the container labels per 21 CFR 201.2.

B. Container Labels (Prefilled Syringe)

1. We note the "M0xxxxx/## US" internal material number competes in prominence with other critical information on the prefilled syringe container labels. We recommend decreasing the font size of the internal material number.

C. Carton Labeling (Prefilled Syringe and Vial)

1. The nonproprietary name is not at least half the size of the proprietary name on the principal display panel and side panel of the branded carton labeling. We refer you to 21 CFR 201.10(g)(2) which states that the nonproprietary name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features. Revise the nonproprietary name to be in accordance with 21 CFR 201.10(g)(2).
2. For consistency with Section 2.1 of the Prescribing Information, we recommend adding the statement, "Bomyntra should be administered by a healthcare provider" or "Denosumab-bnht should be administered by a healthcare provider", to the principal display panel of the Bomyntra branded and unbranded carton labeling.

[a] Bao, A. Label and Labeling Review for Bomyntra (BLA 761398). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2025 Jan 30. TTT ID: 2024-8851.

3. We note the room temperature storage duration indicated on the side panel has been changed from [redacted] (b) (4) to "up to 14 days". Please revise the storage information on the branded and unbranded carton labeling to align with the storage information in the Prescribing Information.
4. We note the "PC" placeholder on the human-readable product information of the branded prefilled syringe carton labeling and unbranded PFS/vial carton labeling has been changed to an NDC number, while the branded vial carton labeling still has a "PC" placeholder. Please confirm if this change is intentional and/or make revisions if needed.

D. Vial Carton Labeling

1. We note the branded and unbranded vial carton submissions contain the note [redacted] (b) (4)
2. We recommend deleting the duplicative "Discard unused portion" statement which appears below the "Sterile Solution – No Preservative" statement on the principal display panel of the unbranded vial carton labeling.
3. We recommend revising "BOMYNTRA" to "Bomyntra" in the storage information of the branded vial carton labeling.

[redacted] (b) (4)

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/s/

AMY J BAO
02/27/2025 01:57:29 PM

YEVGENIYA M KOGAN
02/28/2025 01:44:52 PM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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:	January 30, 2025
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	BLA 761398
Product Name, Dosage Form, and Strength:	Bomyntra (denosumab-bnht) injection, 120 mg/1.7 mL (70 mg/mL)
Product Type:	Single Ingredient Product and Combination Product (Biologic-Device)
Rx or OTC:	Prescription (Rx)
Applicant Name:	Fresenius Kabi USA, LLC
FDA Received Date:	March 25, 2024 and July 3, 2024
TTT ID #:	2024-8851
DMEPA 1 Safety Evaluator:	Amy J. Bao, PharmD, MPH
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 INTRODUCTION

As part of the approval process for Bomyntra (denosumab-bnht) injection, the Division of General Endocrinology (DGE) requested that we review the proposed branded and unbranded Bomyntra Prescribing Information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

Bomyntra (denosumab-bnht) is a proposed 351(k)(4) interchangeable and the US-licensed Reference Product (RP) is Xgeva (denosumab), BLA 125320.

2 MATERIALS REVIEWED

This section lists the materials considered for our review of BLA 761398.

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

3 CONCLUSION

The proposed Bomyntra Prescribing Information (PI), container labels, 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 General Endocrinology (DGE) in Section 4 and for Fresenius Kabi USA, LLC in Section 5.

Note that DMEPA 1 is evaluating the HF validation study results under separate cover and based on the outcome of that review, additional label and labeling comments may be forthcoming.

4 RECOMMENDATIONS FOR THE DIVISION OF GENERAL ENDOCRINOLOGY (DGE)

A. Prescribing Information

1. Section 2 Dosage and Administration – Section 2.5

a. Capitalize “vial” in “Instructions for Bomyntra vial” subheader

b. All relevant figures

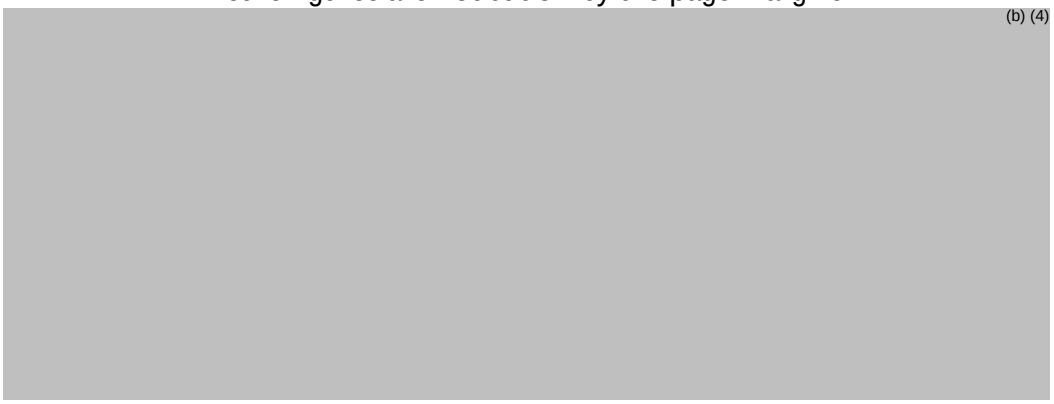
i. Update device labels to say “Bomyntra” instead of “Tradename”

ii. Update the product strength to read “120 mg/1.7 mL (70 mg/mL)”

iii. Align the expiration date shown in the figures to match the format of the expiration date used on the container labels and carton labeling

iv. Ensure figures are not cut off by the page margins

(b) (4)



g. Step 4.1 – Delete text after “Put used prefilled syringe in a sharps disposal container right away after use (see Figure Q).” as it is not relevant to healthcare professionals.

5 RECOMMENDATIONS FOR FRESENIUS KABI USA, LLC

Note that additional label and labeling comments may be forthcoming when we have completed our evaluation of your human factors validation study results.

A. General Comments (Container Labels and Carton Labeling)

1. As currently presented, the proprietary name is denoted by the placeholders "Tradename" and "Proprietary Name". We are unable to assess the prominence and readability of the intended presentation of the proprietary name. We reference our June 21, 2024 Proprietary Name Request Conditionally Acceptable letter informing you that the proprietary name, Bomyntra, was found conditionally acceptable. We recommend replacing the placeholders "Tradename" and "Proprietary Name" with the conditionally acceptable proprietary name, Bomyntra, and use the intend-to-market presentation of the proprietary name (font, color, etc.) so that we may adequately evaluate your labels and labeling.
2. Please refer to the General Advice Letter, dated January 2, 2025, which notified you of the nonproprietary name found conditionally acceptable for your proposed product. Should your BLA be approved during this review cycle, "denosumab-bnht" will be the proper name designated in the license. Revise the nonproprietary name on all labeling to incorporate the FDA-designated nonproprietary name suffix, "-bnht", appended to the core name, "denosumab", so that the proper name appears as "denosumab-bnht" throughout the labeling. See *Draft Guidance for Industry: Nonproprietary Naming of Biological Products: Update (March 2019)*.
3. The nonproprietary name is not at least half the size of the proprietary name. We refer you to 21 CFR 201.10(g)(2) which states that the nonproprietary name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features. Revise the nonproprietary name to be in accordance with 21 CFR 201.10(g)(2).
4. We note an inconsistent and nonstandard use of spaces (e.g., before and after the forward slash, between "120" and "mg", between "1.7" and "mL", etc.) in the formatting of the strength. We recommend standardizing all strength statements as follows: "120 mg/1.7 mL (70 mg/mL)"
5. There is inadequate differentiation between the 60 mg/mL and 120 mg/1.7 mL product strengths (b) (4). Lack of adequate differentiation may contribute to wrong strength medication errors. We recommend using different colors, boxing, or some other means to ensure adequate differentiation between the strengths for the container labels and carton labeling. See *Guidance for*

Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).

6. As currently presented, the expiration date format appears as YYYY-MM. Two letter abbreviations have led to confusion for the months of March vs. May and June vs July. Please clarify whether MM is intended to indicate a 2-letter abbreviation (e.g., JU) for the month or 2-digit (e.g., 01). 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 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)*.

7. We recommend unbolding the "Rx only" statement, and ensuring that the font size of the "Rx only" and NDC are not larger than the size of critical information such as the proprietary name, established name, product strength, lot number, and expiration date.

B. Container Labels (General)

1. Please provide clarification on what the "M0xxxxx/01 US" represents and whether it is necessary to include on the container labels. We recommend deleting this text as it may be mistaken for the lot number.

C. Vial Container Labels

1. The linear barcode is oriented in a horizontal position on the small container. 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. We recommend reorienting the linear barcode on the container label to a vertical position to improve the scannability of the barcode.

2. We note the size of the vial container label may be too small to accommodate all of the information currently presented in a manner that is legible. Critical information such as the established name and strength of the product may be difficult for users to read if small labels are overcrowded with information. We recommend considering removing non-critical information (e.g., "1.7 mL") to allow space for required information to appear in a larger font size. We also recommend adding the "Single-dose vial. Discard unused portion." statement back to the container label to minimize the risk of wrong technique medication errors during preparation of the product. Consider removing "Sterile Solution –

No Preservative" if there is not enough space. At a minimum, the following information must be kept on small container labels:

a. Proprietary name
b. Established name
c. Product strength
d. Lot number
e. Expiration date
f. Name of manufacturer, packer, or distributor
g. Linear barcode

See *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)*.

D. Prefilled Syringe Container Labels

1. As currently presented, the proprietary name lacks prominence on the principal display panel. 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 principal display panel (PDP). We recommend increasing the prominence of the proprietary name and established name. Consider the use of different font type or size, bolding, color, or other means to achieve increased prominence. See *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)*.

2. We note the size of the prefilled syringe container label may be too small to accommodate all of the information currently presented in a manner that is legible. Critical information such as the established name and strength of the product may be difficult for users to read if small labels are overcrowded with information. We recommend considering removing non-critical information (e.g., "1.7 mL" and "Sterile Solution – No Preservative") to allow space for required information to appear in a larger font size. At a minimum, the following information must be kept on small container labels:

   a. Proprietary name
   b. Established name
   c. Product strength
   d. Lot number
   e. Expiration date
   f. Name of manufacturer, packer, or distributor
   g. Linear barcode

   See *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)*.

E. Carton Labeling (General)

1. We recommend removing the "Refrigerate Immediately" statement from the carton labeling as the intent of this statement is unclear and duplicative with the storage information.

2. We recommend revising the statement of dosage from “Dose and Administration: Recommended Dosage: See Prescribing Information.” to “Recommended Dosage: See Prescribing Information.” for improved clarity.
3. The “store refrigerated” statement is not bolded. Not including a bolded “Store refrigerated” statement may result in the risk of the storage information being overlooked and lead to deteriorated drug medication errors. We recommend revising and bolding the storage statement to read “Storage: Store refrigerated at 36°F to 46°F (2°C to 8°C) in the original carton to protect from light.”
4. The abbreviation used for “serial number” on the carton labeling is not one of the abbreviations recommended in the FDA Guidance for Industry on product identifiers required under the Drug Supply Chain Security Act (DSCSA). We recommend updating the abbreviation “SN” to “S/N” or one of the other FDA-recommended abbreviations for serial number. See *Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021)*.
5. We recommend deleting the following, as a beyond-use date area is not relevant for healthcare provider administration:
“Use the space below to record the date the TRADENAME [vial/prefilled syringe] is removed from the refrigerator
[Vial/Prefilled syringe]: _____/_____”
6. We note there is a linear barcode on the side panel which contains the human readable information (product code, serial number, lot number, and expiration date) that appears to be crossed out, please confirm that this will not be printed on the side panel, as it may be mistaken for the linear barcode on the back panel.

F. Vial Carton Labeling

1. On the principal display panel, we recommend removing the following statements to decrease clutter: “Carton contains: 1 single dose prefilled vial - discard unused portion 1 Prescribing Information”. On the side panel, under the “Carton contains:” statement, remove “- discard unused portion”, as the discard statement does not need to be stated when listing the contents of the carton.
2. We recommend deleting the “1 x 1.7 mL” statements that appear next to the images of the vial and replacing them with “1 Single-dose vial. Discard unused portion.”.
3. We recommend deleting the (b) (4) (b) (4) (b) (4)
4. We recommend revising “single dose” to “single-dose” throughout the vial carton labeling.

G. Prefilled Syringe Carton Labeling

1. We recommend deleting "- discard unused portion" from the "Carton contains:" section, as the discard statement does not need to be stated when listing the contents of the carton.
2. We recommend revising the statements which appear directly below the strength from (b) (4) to "Single-dose (b) (4). Discard unused portion.", and moving the statements so that they are located below the "For Subcutaneous use only" statement.
3. We recommend revising "single- dose" to "single-dose" throughout the prefilled syringe carton labeling.
4. We note there is a QR code with a cross mark through it with the text "Scan for additional information" on one of the side panels. We also note that the panel this information appears on will be obscured by the "OPEN HERE" sealed panel. Please confirm if this information is intended to be included on the finalized carton labeling, and if so, please clarify what the QR code links to.

APPENDICES: METHODS AND RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 2 presents relevant product information for Bomyntra received on July 3, 2024 from Fresenius Kabi USA, LLC, and the US-licensed Reference Product (RP).

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

Product Name	Bomyntra	Xgeva[a] (BLA 125320)
Initial Approval Date	N/A	June 1, 2010
Nonproprietary Name	denosumab-bnht	denosumab
Indication	• Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors. • Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity. • Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy.	
Dosage Form	injection	
Strength	120 mg/1.7 mL (70 mg/mL)	
Route of Administration	subcutaneous	
Dose and Frequency	Multiple myeloma and bone metastasis from solid tumors: • 120 mg every 4 weeks Giant cell tumor of bone: • 120 mg every 4 weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy Hypercalcemia of malignancy: • 120 mg every 4 weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy	
How Supplied	120 mg/1.7 mL in a single-dose vial (1 vial per carton) 120 mg/1.7 mL in a single-dose prefilled syringe (1 syringe per carton)	120 mg/1.7 mL in a single-dose vial (1 vial per carton)

[a] Xgeva [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. Jun 2020. [cited 2024 Aug 08]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125320s203lbl.pdf.

Table 2. Relevant Product Information for Bomyntra and the US-licensed Reference Product (RP).		
Product Name	Bomyntra	Xgeva[a] (BLA 125320)
Storage	Store in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton. Do not freeze. Once removed from the refrigerator, product must not be exposed to temperatures above 25°C/77°F or direct light and must be used within (b) (4) days. Discard if not used within the (b) (4) days. Do not use after the expiry date printed on the label. Protect from direct light and heat. Avoid vigorous shaking.	Store in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton. Do not freeze. Once removed from the refrigerator, product must not be exposed to temperatures above 25°C/77°F or direct light and must be used within (b) (4) days. Discard if not used within the (b) (4) days. Do not use after the expiry date printed on the label. Protect from direct light and heat. Avoid vigorous shaking.
Container Closure	Single-dose vial, single-dose prefilled syringe	Single-dose vial

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,[b] along with postmarket medication error data, we reviewed the following Bomyntra labels and labeling submitted by Fresenius Kabi USA, LLC.

- Prescribing Information received on July 3, 2024, available from \\CDSESUB1\evsprod\BLA761398\0009\m1\us\114-labeling\114a-draft-label\draft-labeling-text-uspi-medication-guide-1-7-ml-brand-anno.docx
- Unbranded Prescribing Information received on July 3, 2024, available from \\CDSESUB1\evsprod\BLA761398\0009\m1\us\114-labeling\114a-draft-label\draft-labeling-text-uspi-medication-guide-1-7-ml-unbranded.docx
- Container labels received on March 25, 2024
- Carton labeling received on March 25, 2024
- Unbranded Container labels received on March 25, 2024
- Unbranded Carton labeling received on March 25, 2024

B.2 Container Labels and Carton Labeling Images

Vial Container Labels

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

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

APPENDIX C. PREVIOUS DMEPA REVIEWS

On September 3, 2024, we searched for previous DMEPA reviews relevant to this current review using the term, "denosumab". Our search identified eight previous reviews, and we considered our previous recommendations to see if they are applicable for this current review.

Table 3. List of Previous DMEPA Reviews for denosumab

Application #	Product name	Applicant	Strength	Status	Previous DMEPA Reviews
BLA 125320	Xgeva (denosumab) injection	Amgen, Inc.	120 mg/1.7 mL (70 mg/mL)	Approved 06/01/2010	2010-1310 2014-1786 2017-774
BLA 761362	Wyost (denosumab-bbdz) injection	Sandoz Inc.	120 mg/1.7 mL (70 mg/mL)	Approved 03/05/2024	2023-4809 2023-4809-1
BLA 761404	Osenvelt (denosumab-xxxx) injection	Celltrion, Inc.	120 mg/1.7 mL (70 mg/mL)	Application is pending	2023-7435 2023-7435-1 2023-7435-2
BLA 761398	Bomyntra (denosumab-bnht) injection	Fresenius Kabi USA, LLC	120 mg/1.7 mL (70 mg/mL)	Subject of this review	2024-8851

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/s/

AMY J BAO
01/30/2025 10:20:07 AM

YEVGENIYA M KOGAN
01/31/2025 08:43:57 AM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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:	January 30, 2025
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	BLA 761398
Product Name, Dosage Form, and Strength:	Conexxence (denosumab-bnht) injection, 60 mg/mL
Product Type:	Combination Product (Biologic-Device)
Rx or OTC:	Prescription (Rx)
Applicant Name:	Fresenius Kabi USA, LLC
FDA Received Date:	March 25, 2024 and July 3, 2024
TTT ID #:	2024-8850
DMEPA 1 Safety Evaluator:	Amy J. Bao, PharmD, MPH
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 INTRODUCTION

As part of the approval process for Conexxence (denosumab-bnht) injection, the Division of General Endocrinology (DGE) requested that we review the proposed branded and unbranded Conexxence Prescribing Information (PI), Medication Guide (MG), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

Conexxence (denosumab-bnht) is a proposed 351(k)(4) interchangeable and the US-licensed Reference Product (RP) is Prolia (denosumab), BLA 125320.

2 MATERIALS REVIEWED

This section lists the materials considered for our review of BLA 761398.

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

3 CONCLUSION

We evaluated the proposed Conexxence Medication Guide (MG) and determined that it is acceptable from a medication error perspective.

However, the proposed Conexxence Prescribing Information (PI), container labels, and carton labeling may be improved to promote the 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 General Endocrinology (DGE) in Section 4 and for Fresenius Kabi USA, LLC in Section 5.

Note that DMEPA 1 is evaluating the HF validation study results under separate cover and based on the outcome of that review, additional label and labeling comments may be forthcoming.

4 RECOMMENDATIONS FOR THE DIVISION OF GENERAL ENDOCRINOLOGY (DGE)

A. Prescribing Information

1. Section 2 Dosage and Administration – Section 2.4

a. All relevant figures

i. Update device labels to say “Conexxence” instead of “Tradename”

ii. Update the product strength to read “60 mg/mL”

iii. Align the expiration date shown in the figures to match the format of the expiration date used on the container labels and carton labeling

b. Step 1.1 – Update (b) (4) to “15 to 30 minutes” in the italicized text and in Figure A to align with the rest of Section 2.4

c. Step 1.1 – Update directions to indicate that this step is optional (e.g., “you may remove” or add “(this step is optional)”)

5 RECOMMENDATIONS FOR FRESENIUS KABI USA, LLC

Note that additional label and labeling comments may be forthcoming when we have completed our evaluation of your human factors validation study results.

A. General Comments (Container Labels and Carton Labeling)

1. As currently presented, the proprietary name is denoted by the placeholders "Tradename" and "Proprietary Name". We are unable to assess the prominence and readability of the intended presentation of the proprietary name. We reference our June 18, 2024 Proprietary Name Request Conditionally Acceptable letter informing you that the proprietary name, Conexxence, was found conditionally acceptable. We recommend replacing the placeholders "Tradename" and "Proprietary Name" with the conditionally acceptable proprietary name, Conexxence, and use the intend-to-market presentation of the proprietary name (font, color, etc.) so that we may adequately evaluate your labels and labeling.
2. Please refer to the General Advice Letter, dated January 2, 2025, which notified you of the nonproprietary name found conditionally acceptable for your proposed product. Should your BLA be approved during this review cycle, "denosumab-bnht" will be the proper name designated in the license. Revise the nonproprietary name on all labeling to incorporate the FDA-designated nonproprietary name suffix, "-bnht", appended to the core name, "denosumab", so that the proper name appears as "denosumab-bnht" throughout the labeling. See *Draft Guidance for Industry: Nonproprietary Naming of Biological Products: Update (March 2019)*.
3. The nonproprietary name is not at least half the size of the proprietary name. We refer you to 21 CFR 201.10(g)(2) which states that the nonproprietary name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features. Revise the nonproprietary name to be in accordance with 21 CFR 201.10(g)(2).
4. We note the product strength is currently expressed as "60 mg / 1 mL". Per USP General Chapter <7>, for injectable drug products that hold a volume equal to 1 mL, the strength should be expressed as quantity per milliliter (quantity/mL). Additionally, we note a nonstandard use of spaces (i.e., before and after the forward slash) in the formatting of the strength. We recommend standardizing all strength statements as follows: "60 mg/mL" in accordance with USP General Chapter <7>.
5. There is inadequate differentiation between the 60 mg/mL and 120 mg/1.7 mL product strengths. Lack of adequate differentiation may contribute to wrong strength medication errors. We recommend using different colors, boxing, or

some other means to ensure adequate differentiation between the strengths for the container labels and carton labeling. See *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)*.

6. As currently presented, the expiration date format appears as YYYY-MM. Two letter abbreviations have led to confusion for the months of March vs. May and June vs July. Please clarify whether MM is intended to indicate a 2-letter abbreviation (e.g., JU) for the month or 2-digit (e.g., 01). 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 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)*.
7. We recommend unbolding the "Rx only" statement, and ensuring that the font size of the "Rx only" and NDC are not larger than the size of critical information such as the proprietary name, established name, product strength, lot number, and expiration date.

B. Container Labels

1. Please provide clarification on what the "M0xxxxx/00 US" represents and whether it is necessary to include on the container labels. We recommend deleting this text as it may be mistaken for the lot number.
2. We note the size of the prefilled syringe container label may be too small to accommodate all of the information currently presented in a manner that is legible. Critical information such as the established name and strength of the product may be difficult for users to read if small labels are overcrowded with information. We recommend considering removing non-critical information (e.g., "1 mL" and "Sterile Solution – No Preservative") to allow space for required information to appear in a larger font size. At a minimum, the following information must be kept on small container labels:
    a. Proprietary name
    b. Established name
    c. Product strength
    d. Lot number
    e. Expiration date
    f. Name of manufacturer, packer, or distributor
    g. Linear barcode

See *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)*.

C. 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 adding the statement "Must be administered by a healthcare provider" to the principal display panel of the carton labeling. The statement will 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. We recommend deleting "- discard unused portion" from the "Carton contains:" section, as the discard statement does not need to be stated when listing the contents of the carton.
3. We recommend revising the statements which appear directly below the strength from (b) (4) (b) (4) Discard unused portion.", and moving the statements so that they are located below the "For Subcutaneous use only" statement.
4. We also recommend revising "Single- dose" or "single dose" to "Single-dose" throughout the carton labeling.
5. We recommend removing the "Refrigerate Immediately" statement from the carton labeling as the intent of this statement is unclear and duplicative with the storage information.
6. We recommend revising the statement of dosage from "**Dose and Administration:** Recommended Dosage: See Prescribing Information." to "**Recommended Dosage:** See Prescribing Information." for improved clarity.
7. The "store refrigerated" statement is not bolded. Not including a bolded "Store refrigerated" statement may result in the risk of the storage information being overlooked and lead to deteriorated drug medication errors. We recommend revising and bolding the storage statement to read "**Storage: Store refrigerated** at 36°F to 46°F (2°C to 8°C) in the original carton to protect from light."
8. The abbreviation used for "serial number" on the carton labeling is not one of the abbreviations recommended in the FDA Guidance for Industry on product identifiers required under the Drug Supply Chain Security Act (DSCSA). We recommend updating the abbreviation "SN" to "S/N" or one of the other FDA-recommended abbreviations for serial number. See *Guidance for Industry:*

Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021).

9. We recommend deleting the following, as a beyond-use date area is not relevant for healthcare provider administration:
   "Use the space below to record the date the TRADENAME prefilled syringe is removed from the refrigerator
   Prefilled syringe: _____/_____"

10. We note there is a linear barcode on the side panel which contains the human readable information (product code, serial number, lot number, and expiration date) that appears to be crossed out, please confirm that this will not be printed on the side panel, as it may be mistaken for the linear barcode on the back panel.

11. We note there is a QR code with a cross mark through it with the text "Scan for additional information" on one of the side panels. We also note that the panel this information appears on will be obscured by the "OPEN HERE" sealed panel. Please confirm if this information is intended to be included on the finalized carton labeling, and if so, please clarify what the QR code links to.

APPENDICES: METHODS AND RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 2 presents relevant product information for Conexxence received on July 3, 2024 from Fresenius Kabi USA, LLC, and the US-licensed Reference Product (RP).

Table 2. Relevant Product Information for Conexxence and the US-licensed Reference Product (RP).		
Product Name	Conexxence	Prolia[a] (BLA 125320)
Initial Approval Date	N/A	June 1, 2010
Nonproprietary Name	denosumab-bnht	denosumab
Indication	• Treatment of postmenopausal women with osteoporosis at high risk for fracture • Treatment to increase bone mass in men with osteoporosis at high risk for fracture • Treatment of glucocorticoid-induced osteoporosis in men and women at high risk for fracture • Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer • Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer	
Dosage Form	injection	
Strength	60 mg/mL	
Route of Administration	Subcutaneous	
Dose and Frequency	60 mg every 6 months	
How Supplied	Single-dose prefilled syringe with an automatic clear needle safety guard	Single-dose prefilled syringe with a safety guard. The prefilled syringe is not made with natural rubber latex.

[a] Prolia [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. Mar 2024. [cited 2024 Sep 18]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/125320s213lbl.pdf

Table 2. Relevant Product Information for Conexxence and the US-licensed Reference Product (RP).		
Product Name	Conexxence	Prolia[a] (BLA 125320)
Storage	Store in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton. Do not freeze. Prior to administration, may be allowed to reach room temperature (up to 25°C/77°F) in the original container. Once removed from the refrigerator, must not be exposed to temperatures above 25°C/77°F and must be used within (b) (4) days. Discard if not used within (b) (4) days. Do not use after the expiry date printed on the label. Protect from direct light and heat. Avoid vigorous shaking.	Store in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton. Do not freeze. Prior to administration, may be allowed to reach room temperature (up to 25°C/77°F) in the original container. Once removed from the refrigerator, must not be exposed to temperatures above 25°C/77°F and must be used within (b) (4) days. Discard if not used within the (b) (4) days. Do not use after the expiry date printed on the label. Protect from direct light and heat. Avoid vigorous shaking.
Container Closure	Single-dose prefilled syringe	

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,[b] along with postmarket medication error data, we reviewed the following Conexxence labels and labeling submitted by Fresenius Kabi USA, LLC.

- Prescribing Information received on July 3, 2024, available from \\CDSESUB1\evsprod\BLA761398\0009\m1\us\114-labeling\114a-draft-label\draft-labeling-text-uspi-and-medication-guide-1ml-60-mg-pfs.docx
- Unbranded Prescribing Information received on July 3, 2024, available from \\CDSESUB1\evsprod\BLA761398\0009\m1\us\114-labeling\114a-draft-label\draft-labeling-text-uspi-and-medication-guide-1ml-unbranded.docx
- Medication Guide received on July 3, 2024, available from \\CDSESUB1\evsprod\BLA761398\0009\m1\us\114-labeling\114a-draft-label\draft-labeling-text-uspi-and-medication-guide-1ml-60-mg-pfs.docx
- Unbranded Medication Guide received on July 3, 2024, available from \\CDSESUB1\evsprod\BLA761398\0009\m1\us\114-labeling\114a-draft-label\draft-labeling-text-uspi-and-medication-guide-1ml-unbranded.docx
- Branded and unbranded container labels received on March 25, 2024
- Branded and unbranded carton labeling received on March 25, 2024

B.2 Container Labels and Carton Labeling Images

Container labels

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

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APPENDIX C. PREVIOUS DMEPA REVIEWS

On September 18, 2024, we searched for previous DMEPA reviews relevant to this current review using the term, "denosumab". Our search identified 11 previous reviews, and we considered our previous recommendations to see if they are applicable for this current review.

Table 3. List of Previous DMEPA Reviews for denosumab

Application #	Product name	Applicant	Strength	Status	Previous DMEPA Reviews
BLA 125320	Prolia (denosumab) injection	Amgen, Inc.	60 mg/mL	Approved 06/01/2010	2011-4679 2011-4679-1 2016-2303 2016-1751 2017-1903 2022-2530
BLA 761362	Jubbonti (denosumab-bbdz) injection	Sandoz Inc.	60 mg/mL	Approved 03/05/2024	2022-2980 2022-2980-1
BLA 761404	Stoboclo (denosumab-bmwo) injection	Celltrion, Inc.	60 mg/mL	Application is pending	2023-7341 2023-7341-1 2023-7341-2
BLA 761398	Conexxence (denosumab-bnht) injection	Fresenius Kabi USA, LLC	60 mg/mL	Subject of this review	2024-8850

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YEVGENIYA M KOGAN
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USE-RELATED RISK ANALYSIS AND HUMAN FACTORS STUDY RESULT REPORT REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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:	January 24, 2025
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	BLA 761398
Product Type:	Combination Product (Biologic-Device)
Product Name, Dosage Form and Strength:	Bomyntra[a] (denosumab-bnht)[b] injection, 120 mg/1.7 mL (70 mg/mL)
Device Constituent:	Pre-Filled Syringe
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Fresenius Kabi USA, LLC
FDA Received Date:	March 25, 2024, May 09, 2024, July 03, 2024
TTT #:	2024-8853
DMEPA 1 Safety Evaluator:	Florence Mwangi, PharmD
DMEPA 1 Team Leader:	Matthew Barlow, RN, BSN
DMEPA 1 Associate Director for Human Factors:	Ariane O. Conrad, PharmD, BCACP, CDCES, FISMP

[a] Fresenius Kabi refers to the proposed product as "FKS518" throughout their submission. FKS518 was developed as a proposed interchangeable biosimilar to US-licensed Prolia (hereafter called Prolia). Of note, Fresenius Kabi submitted the proposed proprietary name Bomyntra (denosumab-xxxx) for review on March 25, 2024 (PNR ID# 2024-1044725698). The proprietary name, Bomyntra, was found conditionally acceptable on June 13, 2024. For the purposes of this review, "FKS518" is used throughout the review to refer to this product.

[b] The nonproprietary name suffix (denosumab-bnht) for this BLA was found conditionally acceptable on December 20, 2024.

1 REASON FOR REVIEW

This review evaluates the use-related risk analysis (URRA), threshold analysis (hereafter referred to as comparative analyses), and human factors (HF) validation study results submitted under Biologic License Application (BLA) 761398 for FKS518 injection 120 mg/1.7 mL prefilled syringe (PFS) a proposed interchangeable biosimilar to US-licensed Xgeva (denosumab)[c]. Of note, Xgeva is currently approved as a 120 mg/1.7 mL single-dose vial. While we acknowledge that data from an HF validation study would not be the appropriate HF data to support interchangeability, we conducted a high-level review of the HF validation study results.

Additionally, we note that Fresenius Kabi submitted a use-related risk analysis (URRA), comparative analyses, and justification for not submitting HF validation study results to support their marketing application for FKS518 60 mg/mL PFS, a proposed interchangeable biosimilar to US licensed Prolia, which was reviewed under a separate cover.[d]

1.1 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review.

Table 1. Materials Considered for this Review

Material Reviewed	Section/Appendix
Product Information	Section 1.2
Background Information Previous Relevant HF Reviews (DMEPA)	Section 1.3
Human Factors (HF) Validation Study Report, Use-Related Risk Analysis (URRA) and HF-Related Supporting Documents	Appendix A
Information Requests Issued During the Review	Appendix B
Product sample, Labels, Labeling, and Packaging	Appendix C

[c] Referred to as Xgeva throughout the review.

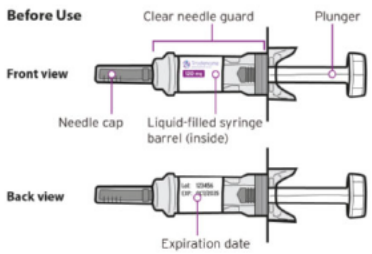
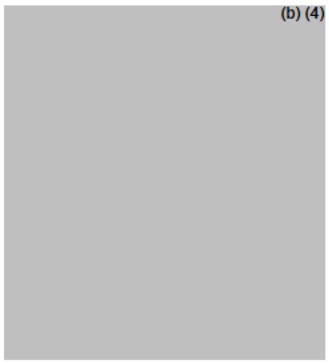
[d] Mwangi, F. Conexxence (denosumab-bnht) 60 mg PFS URRA and CA Review Memo (BLA 761398). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2025 JAN 24. TTT No.: 2024-9240

1.2 PRODUCT INFORMATION

Table 2 presents relevant product information for Bomyntra that Fresenius Kabi USA, LLC submitted on March 25, 2024 and July 3, 2024 and for US-Licensed Xgeva.

Table 2. Relevant Product Information for Bomyntra and Reference Product Xgeva[e]		
	Bomyntra	US-Licensed Xgeva
Initial Approval Date	N/A	June 01, 2010
Non Proprietary name	denosumab-bnht	denosumab
Indication	• Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors. • Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity. • Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy	
Route of Administration	Subcutaneous	
Dosage Form	Injection	
Strength	120 mg/1.7 mL (70 mg/mL)	
Dose and Frequency	<u>Multiple Myeloma and Bone Metastasis from Solid Tumor:</u> 120 mg every 4 weeks <u>Giant Cell Tumor of Bone:</u> 120 mg every 4 weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy <u>Hypercalcemia of Malignancy:</u> 120 mg every 4 weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy	
How Supplied	FKS518 is supplied in a single-dose prefilled syringe (PFS) with a safety guard and in a single-dose vial. • 120 mg/1.7 mL in a single-dose vial 1 vial per carton	Xgeva is supplied in a single dose vial • 120 mg/1.7 mL in single-dose vial 1 vial per carton

[e] Xgeva [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. Feb 2020. [cited 2024 Sep 3]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125320s201lbl.pdf

	• 120 mg/1.7 mL in a single-dose PFS 1 syringe per carton	
Storage	Store FKS518 in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton. Do not freeze. Once removed from the refrigerator, FKS518 must not be exposed to temperatures above 25°C/77°F or direct light and must be used within (b) (4) days. Discard FKS518 if not used within the (b) (4) days. Do not use FKS518 after the expiry date printed on the label. Protect FKS518 from direct light and heat. Avoid vigorous shaking of FKS518.	Store Xgeva in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton. Do not freeze. Once removed from the refrigerator, Xgeva must not be exposed to temperatures above 25°C/77°F or direct light and must be used within (b) (4) days. Discard Xgeva if not used within the (b) (4) days. Do not use Xgeva after the expiry date printed on the label. Protect Xgeva from direct light and heat. Avoid vigorous shaking of Xgeva.
Container Closure/ Device Constituent (including figure)	Nemera -Safe'n' Sound platform device (single dose prefilled syringe) 	Single dose vial 
Intended Users	Healthcare Professional	
Intended Use Environment	Clinical (hospital, physician's office)	
Other important HF-related information relevant for this review	The reference product, Xgeva, is currently approved as a vial only for use by HCPs only. Fresenius Kabi submitted a URRA, comparative analyses, and HF validation study results to support their marketing application for FKS518 120 mg/1.7 mL in a PFS presentation as an interchangeable biosimilar to Xgeva 120 mg/1.7 mL vial.	

1.3 RELEVANT REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

On November 4, 2024, we searched for previous DMEPA reviews and FDA/Applicant interactions relevant to this current review using the terms, "*IND 145897*", "*BLA 761398*". The following bullets summarize the regulatory history specific to why Fresenius Kabi submitted the HF validation study results, URRA, and a comparative analyses as part of their marketing application for FKS518 120 mg/1.7 mL PFS.

- On November 18, 2019, Fresenius Kabi submitted a Biosimilar Biological Product Development (BPD) Type 2 meeting request under IND 145897 to obtain the Agency's feedback on the proposed development program for FKS518 quality profile and the clinical development strategy for the proposed biosimilar of Prolia and US-licensed Xgeva. Fresenius Kabi proposed development plans for a FKS518 PFS presentation as a proposed biosimilar to Xgeva, though the reference product Xgeva is marketed in a single-dose vial. In the final meeting minutes dated March 13, 2020, we recommended a comprehensive use-related risk analysis and comparative analysis to determine if Fresenius Kabi needs to submit results of an HF validation study to support their future marketing application for FKS518.[f]
- On May 24, 2022, Fresenius Kabi submitted an HF validation study protocol under IND 145897 for FKS518 120 mg/1.7 mL PFS, a proposed biosimilar to Xgeva, for the same indications as Xgeva for use by patients and caregivers. We reviewed the HF validation study protocol and provided recommendations.[g]
- On November 14, 2023, Fresenius Kabi submitted a BPD Type 4 Meeting Package under IND 145897 for FKS518 120 mg/1.7 mL PFS and FKS518 60 mg/mL PFS which contained questions regarding their plan to conduct an HF validation study to support a patient "*self-administration claim"* for FKS518 120 mg/1.7 mL PFS.
    - Per the February 22, 2024 meeting minutes, Fresenius Kabi was advised that their proposal regarding self-administration would be discussed internally.[h]
    - In the March 06, 2024 general advice letter, the Division of General Endocrinology (DGE) advised Fresenius Kabi that "*we would not anticipate approving your proposed*" FKS518 120 mg/1.7 mL (70 mg/mL) for self-administration because the approved labeling for the reference product Xgeva, does not reflect licensure for self-administration.[i]
- On March 25, 2024, Fresenius Kabi submitted an HF validation study results report, comparative analyses, and URRA under BLA 761398 for FKS518 120 mg/1.7 mL PFS

[f] Bell, S. Type 2 BPD Meeting Minutes for FKS518 (denosumab-xxxx) Injection 120 mg/1.7 mL (70 mg/mL), (IND 145897). Silver Spring (MD): FDA, CDER, OND (DGE); 2020 MAR 13.
[g] Hoon Lee, S. Human Factors Protocol Review for FKS518 (denosumab-xxxx) injection 120 mg/1.7 ml (70 mg/mL) (IND 145897). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2022 JUL 25. OSE RCM No.: 2022-1081.
[h] Cabellon, N. Meeting Minutes for FKS518 (IND 145897). Silver Spring (MD): FDA, CDER, OND (DGE); 2024 FEB 22.
[i] Cabellon, N. General Advice Letter for FKS518 (IND 145897). Silver Spring (MD): FDA, CDER, OND (DGE); 2024 MAR 06.

to support their application as a proposed interchangeable biosimilar to Xgeva for use by healthcare providers (HCPs), which are the subjects of this review.

2 OVERALL ASSESSMENT OF USE-RELATED RISK ANALYSIS & COMPARATIVE ANALYSES

The section below provides our evaluation of the URRA and comparative analyses for the proposed FKS518 120 mg/1.7 mL PFS intended for use by healthcare providers (HCP) only.

Fresenius Kabi submitted a URRA for their FKS518 PFS. The URRA identified and evaluated the tasks involved in the use of the product, the errors that users might commit, the tasks they might fail to perform, and the potential negative consequences of use errors. We reviewed the URRA for FKS518 120 mg/1.7 mL PFS and considered the intended users and intended use environment in our overall assessment. Based on the information we have at this time, the tasks evaluated appear to be comprehensive and appropriate based on what Fresenius Kabi proposes for the design and intended use of this FKS518 120 mg/1.7 mL PFS. For more details regarding the comprehensive URRA see Appendix A.

We acknowledge Fresenius Kabi submitted comparative analyses evaluating the Xgeva vial and the proposed FKS518 PFS in which Fresenius Kabi identified "minor" differences in the physical comparison, labeling comparison, and comparative task analyses. However, our analysis identified several *"other"* design differences in the physical comparison (vial versus PFS presentation), labeling comparison (Section 2.5 preparation and administration of the prescribing information), and comparative task analyses (e.g., attach needle to the syringe, draw medication from the vial into a syringe, and release the plunger, etc.). We note that this presentation difference may be acceptable because there are less tasks, including critical tasks, required for dose preparation with the use of a PFS as compared to a vial. Thus, in this instance, we determined the aforementioned "other" design differences and the related risk associated with this proposed PFS are acceptable and do not present new or unique risks when compared to similar marketed products intended for use by HCPs only.

In addition, we determined the risks are mitigated by the proposed labels and labeling when considering the intended use, intended use environment(s), and intended users (HCPs).

3 HUMAN FACTORS VALIDATION STUDY RESULTS DISCUSSION

Fresenius Kabi conducted a HF validation study for their FKS518 120 mg/1.7 mL PFS to evaluate the use of the PFS user interface by healthcare providers (HCPs). We acknowledge that data from an HF validation study would not be the appropriate HF data to support biosimilar interchangeability. However, we conducted a high-level review of the HF validation study results to identify potential recommendations based on the participants subjective feedback. Fresenius Kabi conducted the HF validation

study with a total of 15 healthcare providers (oncology nurses, hematology oncology nurses, registered nurses, oncologist). The product user interface evaluated in the HF validation study included "*production equivalent*" FKS518 120 mg/1.7 mL PFS with packaging and labeling. Of note, since the Fresenius Kabi is now seeking HCP administration only, the content of the proposed instruction for use (IFU) evaluated in the HF validation study, has been incorporated into Section 2.4 of the proposed prescribing information.

The HF validation study report showed issues with the tasks evaluated by simulated use and knowledge task assessments listed in Appendix D. Based on our review of the available assessment of these identified issues, the available participants' subjective feedback (including when participants' subjective feedback did not indicate any potential issue with the user interface), the Applicant's root cause analysis, and our evaluation of the residual risks and post-HFVS changes to the user interface, we have no additional recommendations to address the identified issues with the tasks in Appendix D.

4 LABELS AND LABELING

Please note that the DMEPA 1 nomenclature and labeling team is evaluating the label and labeling under separate cover.

5 CONCLUSION

Based on review of the URRA and comparative analyses, we determined that Fresenius Kabi does not need to submit comparative use human factors study results with their marketing application for FKS518 120 mg/1.7 mL PFS as a proposed interchangeable biosimilar to Xgeva for use by healthcare providers. As such, we have no additional HF recommendation for this marketing application.

6 APPENDICES:

APPENDIX A. HUMAN FACTORS (HF) VALIDATION STUDY REPORT AND HF-RELATED SUPPORTING DOCUMENTS

The human factors study results report can be accessed in EDR via: \\CDSESUB1\EVSPROD\bla761398\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\osteoporosispmo\5354-other-stud-rep\humanfactorstudyinformation\pfs2-25ml\fksb-r-md-173-01-hfue-for-fks518-deno-2-25ml.pdf

The use-related risk analysis can be accessed in EDR via: \\CDSESUB1\EVSPROD\bla761398\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\osteoporosispmo\5354-other-stud-rep\humanfactorstudyinformation\pfs2-25ml\fksb-ras-md-018-04-urra-for-fks518-deno-2-25ml.pdf

The comparative analyses can be accessed in EDR via: \\CDSESUB1\EVSPROD\bla761398\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\osteoporosispmo\5354-other-stud-rep\humanfactorstudyinformation\pfs2-25ml\fksb-r-md-175-01-ta-for-fks518-deno-2-25ml.pdf

APPENDIX B. INFORMATION REQUESTS ISSUED DURING THE REVIEW

On May 7, 2024, we issued an Information Request (IR) to request which HCP participants in the HF validation study have experience with administering Xgeva. In addition, we requested a complete and comprehensive URRA for FKS518 120 mg/1.7 mL (70 mg/mL). On May 9, 2024, Fresenius Kabi provided an acceptable response that can be accessed in EDR via:

Response to HF IR #1: \\CDSESUB1\EVSPROD\bla761398\0004\m5\53-clin-stud-rep\535-rep-effic-safety-stud\osteoporosispmo\5354-other-stud-rep\humanfactorstudyinformation\pfs2-25ml\response-to-hf-ir-1-received-on-may-07-2024.pdf

Comprehensive URRA: \\CDSESUB1\EVSPROD\bla761398\0004\m5\53-clin-stud-rep\535-rep-effic-safety-stud\osteoporosispmo\5354-other-stud-rep\humanfactorstudyinformation\pfs2-25ml\fksb-ras-md-018-04-appendix-a.pdf

APPENDIX C. PRODUCT SAMPLES, LABELS, LABELING, AND PACKAGING

C.1 Product Sample

The product samples were submitted for our review, and we did not identify any recommendations for improvement at this time.

C.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[j] along with postmarket medication error experiences with similar products, we reviewed the following FKS518 (denosumab) 120 mg/1.7 mL labels and labeling submitted by Fresenius Kabi USA, LLC (Fresenius).

- Container label(s) received on March 25, 2024
- Carton labeling received on March 25, 2024
- Prescribing Information (Image not shown) received on July 03, 2024, available from \\CDSESUB1\EVSPROD\bla761398\0009\m1\us\114-labeling\114a-draft-label\draft-labeling-text-uspi-medication-guide-1-7-ml-brand-anno.docx

C.2 Label and Labeling Images

Container label

Carton labeling

APPENDIX D. DETAILED LIST OF USE ERRORS, USE DIFFICULTIES, AND CLOSE CALLS FROM SECTION 3

Simulated use scenario:

- Check expiration date
- Set carton on flat clean surface and allow to acclimate to room temperature
- Check the expiration date on the device
- Check the product name on the label
- Check the device integrity
- Check integrity of the drug
- Select and injection site (must be different from the previous injection site)
- Remove the needle cap - there were two (2) use errors in the IFU optional scenario with this task in which participants pressed the plunger after removing the needle cap to expel bubbles prior to the injection. The error was attributed to negative transfer due to clinical practice of the HCP participants. Fresenius Kabi stated that further changes to the IFU would not have mitigated this error; therefore no further modifications were proposed by Fresenius Kabi. Based on our review of the user interface, we did not identify any additional mitigations to address this use error and have no recommendations at this time._

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

- Pinch the skin - there was one (1) use error in the IFU optional scenario with this task in which one participant did not pinch the skin while injecting. The participant did not pinch the skin because they knew they were injecting into an injection pad. Fresenius Kabi attributed the error to test artifact as they would not expect, this error to occur during actual use. Therefore, no modifications were proposed by Fresenius Kabi. Based on our review of the user interface, we did not identify any additional mitigations to address this use error and have no recommendations at this time.
- Press the plunger down until all the drug has been injected - there was one (1) use error in the IFU optional scenario with this task in which one participant tried to press the plunger further down after injection. The participant expected to hear a click because they read in the IFU that there might be a click after pressing the plunger, which the participant did not notice or hear. The IFU states that a click "may" be heard or felt. This participant successfully administered the full injection during this scenario and the following IFU mandatory scenario without difficulty; therefore, no modifications were proposed by Fresenius Kabi. Based on our review of the user interface, we did not identify any additional mitigations to address this use error and have no recommendations at this time.
- Release pressure from the plunger rod which activates the safety system.

Knowledge assessments:

- What should you do, or not do, if either: the carton is opened or damaged, the prefilled syringe has been dropped on a hard surface? Answer-do not use prefilled syringe. Use a new prefilled syringe.
- When should you push the plunger rod of the prefilled syringe? Answer-only when ready to administer the injection with the syringe. Do not try to push the plunger rod of the prefilled syringe before the injection.
- From what should you protect the medicine when storing? Answer-direct light or heat
- What should you not do when warming the prefilled syringe at room temperature? Answer-Do not try to warm the prefilled syringe by using a heat source as hot water or microwave
- There are certain things you should check before using the prefilled syringe. In which cases should you not use the prefilled syringe? Answer- the name on the label is not tradename. The expiration date on the label has passed. Any part appears cracked or broken. The needle cap is missing or not firmly attached. The medicine is cloudy or there are particles in it. It must be a clear, colorless to slightly yellow solution.
- What areas are considered acceptable injection sites? Answer-upper thigh, belly (except for a 2-inch (5 cm) area around the belly button), outer area upper arm.
- What areas should you not inject into? Answer-areas where the skin is tender, bruised, red or hard. Avoid injection into areas with scars or stretch marks.
- What should you not do when removing the needle cap? Answer- do not remove the needle cap from the prefilled syringe until you are ready to inject. Do not hold the prefilled syringe by the plunger rod.
- After you have removed the needle cap, what should you do and not do? Answer-throw away (dispose of) the needle cap in your sharps disposal container. Do not put the needle

cap back onto the prefilled syringe. Do not touch the needle or let it touch any surface after removal of the needle cap.

- At what angle should you inject the needle? Answer- 45° to 90° angle
- What do you do after you have pushed the plunger all the way down and have injected all the liquid under the skin? Answer- release the plunger (which allows the needle to come out of the skin and clear needle guard to cover the needle.

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/

FLORENCE W MWANGI
01/24/2025 05:53:18 PM

MATTHEW J BARLOW
01/24/2025 05:56:45 PM

ARIANE O CONRAD
01/24/2025 06:11:31 PM

MEMORANDUM

USE-RELATED RISK ANALYSIS AND COMPARATIVE ANALYSES REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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:	January 24, 2025
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	BLA 761398
Product Type:	Combination Product (Drug-Device)
Product, Name, Dosage Form and Strength:	Conexxence[a] (denosumab-bnht)[b] injection, 60 mg/mL
Device Constituent:	Prefilled Syringe (PFS)
Rx or OTC:	Prescription (Rx)
Applicant/Applicant Name:	Fresenius Kabi USA, LLC (Fresenius Kabi)
FDA Received Date:	March 25, 2024, May 09, 2024, July 03, 2024
OSE TTT #:	2024-9240
DMEPA 1 Safety Evaluator:	Florence Mwangi, PharmD
DMEPA 1: Team Leader:	Matthew Barlow, RN, BSN
DMEPA 1 Associate Director for Human Factors:	Ariane O. Conrad, PharmD, BCACP, CDCES

[a] FKS518 has been developed as a proposed interchangeable biosimilar to US-licensed Prolia. The proprietary name Conexxence was found conditional acceptable by DMEPA on June 12, 2024. For the purposes of this review, "FKS518" is used throughout the review to refer to this product.

[b] The nonproprietary name suffix (denosumab-bnht) for this BLA was found conditionally acceptable on December 20, 2024.

1 REASON FOR REVIEW

On March 25, 2024, the Applicant submitted a Biologics License Application (BLA) 761398 that included a use-related risk analysis (URRA), threshold analysis (hereafter referred to as comparative analyses), and justification to support their marketing application for FKS518 (denosumab-xxxx) 60 mg/mL prefilled syringe (PFS) as a proposed interchangeable biosimilar to US-licensed Prolia (hereafter referred to as Prolia). This review focuses on the URRA, CA, and justification for not submitting HF validation study data for the FKS518 60 mg/mL PFS.

Of note, the Applicant also submitted an URRA and HF validation study results report for FKS518 (denosumab-xxxx) 120 mg/1.7 mL (70 mg/mL) PFS, as a proposed interchangeable biosimilar to US-licensed Xgeva (hereafter referred to as Xgeva), which was reviewed under a separate cover.[c]

2 BACKGROUND

FKS518 60 mg/mL is a single ingredient combination product with a single-dose prefilled syringe device constituent part, intended for administration by healthcare professionals. FKS518 is a receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor proposed for:

- Treatment of postmenopausal women with osteoporosis at high risk for fracture
- Treatment to increase bone mass in men with osteoporosis at high risk for fracture
- Treatment of glucocorticoid-induced osteoporosis in men and women at high risk for fracture
- Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer
- Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer

On November 18, 2019, the Applicant submitted a Biosimilar Biological Product Development (BPD) Type 2 Meeting request under IND 145897 for FKS518, to obtain the Agency's feedback on the proposed development program regarding the FKS518 quality profile and the clinical development strategy for FKS518 as a proposed biosimilar of Prolia and Xgeva.

- The Applicant proposed development plans for a PFS presentation for the proposed Xgeva and Prolia biosimilar.
- The Applicant provided their human factors engineering plan for the FKS518 60 mg/mL PFS presentation and stated that a comprehensive use-related risk analysis (URRA) will be conducted and submitted for Agency review and feedback.[d]

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[c] Mwangi F. Bomyntra (denosumab-bnht) injection 120 mg/1.7 mL (70 mg/mL) PFS URRA and HF results review (BLA 761398). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2025 JAN 24. TTT No.: 2024-8853

[d] Type 2 BPD Meeting Package for FKS518 (denosumab-xxxx) Injection 120 mg/1.7 mL (70 mg/mL), (IND 145897). Fresenius Kabi, 2019 NOV 18. Available from: \\CDSESUB1\evsprod\ind145897\0001\m1\us\16-meetings\meeting-request-000044379.pdf

- In the final meeting minutes dated March 13, 2020, we provided additional human factors comments on the submission of the comprehensive URRA.[e]

On May 13, 2022, the Applicant submitted a URRA, CA, and justification for not submitting HF validation study results under IND 145897 for FKS518 60 mg/mL PFS to support their future marketing application as a proposed biosimilar to Prolia. On August 23, 2022, we reviewed the URRA, CA, and justification and determined that the Applicant does not need to submit HF validation study results to support their future marketing application for FKS518 60 mg/mL PFS as a proposed biosimilar to Prolia. We also advised the Applicant that if they modified their product user interface, that they will need to submit an updated URRA with a determination for HF data requirements for Agency review.[f]

On March 25, 2024, the Applicant submitted their marketing application under BLA 761398 for FKS518 60 mg/mL PFS as a proposed interchangeable biosimilar to Prolia. This submission included their URRA, CA, and justification for not submitting HF validation study results for FKS518 60 mg/mL PFS. However, it was not clear if the product user interface of the proposed FKS518 60 mg/mL PFS presentation submitted under BLA 761338 was identical to the product user interface of the proposed FKS518 60 mg/mL PFS evaluated in the URRA, CA and justification submitted on May 13, 2022 under IND 145897.

On May 07, 2024, we issued an HF information request (IR) to clarify if the product user interface URRA, CA, and justification of the proposed FKS518 60 mg/mL PFS submitted under IND 145897 on May 13, 2022 was identical to the product user interface, URRA, and CA submitted under BLA 761338 on March 25, 2024. On May 09, 2024, the Applicant confirmed that the FKS518 60 mg/mL PFS product user interface is the same with one exception: the "*Blister lid and consequently blister label were eliminated from the user interface of the proposed FKS518 (denosumab-xxxx) submitted in 2024*." The Applicant also stated that "*reducing the required number of user tasks might reduce complexity of the user interface and minimize risks related to delayed therapy*." Additionally, the Applicant indicated that the information in the Prolia blister cover (e.g., proprietary, and established name, dosage form, strength, route, lot number, expiration date, storage and handling) is provided in the FKS518 60 mg/mL PFS carton labeling.

The Applicant indicated that they made the following changes to the CA since our August 2022 review:

- Updated the physical comparison and labeling to reflect the change with the elimination of the blister cover and label.
- Changed minor wording and clarifications to the general sections of the CA,

[e] Bell, S. Type 2 BPD Meeting Minutes for FKS518 (denosumab-xxxx) Injection 120 mg/1.7 mL (70 mg/mL), (IND 145897). Silver Spring (MD): FDA, CDER, OND (DGE); 2020 MAR 13.

[f] Birkemeier, D. Use-Related Risk Analysis and Comparative Analyses review for FKS518 (denosumab) Injection, 60 mg/mL (IND 145897). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US);23 AUG 2022. OSE RCM No.: 2022-955

Additionally, the Applicant stated they made the following changes to the URRA since our August 2022 review:

- Updated the URRA to include risk acceptability post-mitigation to show the risk acceptability categories for all identified risks post-mitigation.
- Updated the URRA to re-organize the order of use steps in the critical task analysis to better represent the use steps in actual use.
- Updated the URRA Section 11 to include a summary of the comparative analyses
- Updated the following information in Appendix a-FMEA of the URRA to update with new available information:
    - Verification of implementation and effectiveness of risk control measures.
    - Completed the risk post-mitigation section.
    - Completed the individual-benefit-risk ratio section.

Of note, the Applicant also stated that they updated the packaging and labeling of the FKS518 60 mg/mL PFS to incorporate labeling feedback received from the Agency for other previously submitted products. The DMEPA 1 nomenclature and labeling review team will evaluate product specific label and labeling under a separate cover.

Based on our independent expert review of the aforementioned information, we determined that these CA, URRA, and labeling differences are unlikely to negatively impact user's ability to complete the critical tasks needed to use this product safely and effectively in the context of a proposed interchangeable biosimilar product to Prolia. Therefore, we determine that these labeling differences do not warrant data from a comparative use human factors (CUHF) study.

3 CONCLUSION

Based on the aforementioned information, we determined that the Applicant does not need to submit comparative use human factors (CUHF) study results with their marketing application for FKS518 (denosumab-xxxx) 60 mg/mL PFS as a proposed interchangeable biosimilar to Prolia. We have no HF recommendations for this marketing application.

Note that the DMEPA 1 nomenclature and labeling team is evaluating the labels and labeling under a separate cover and, based on the outcome of that review, additional label and labeling comments may be forthcoming.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. USE-RELATED RISK ANALYSIS AND COMPARATIVE ANALYSES

The use-related risk analysis can be accessed in EDR via:
\\CDSESUB1\EVSPROD\bla761398\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\osteoporosispmo\5354-other-stud-rep\humanfactorstudyinformation\pfs1ml\fksb-ras-md-017-03-urra-for-fks518-deno-1ml.pdf

The comparative analysis can be accessed in EDR via:
\\CDSESUB1\EVSPROD\bla761398\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\osteoporosispmo\5354-other-stud-rep\humanfactorstudyinformation\pfs1ml\fksb-r-md-096-02-ta-for-fks518-deno-1ml.pdf

APPENDIX B. HUMAN FACTORS ENGINEERING REPORTS

The HF-UE Report (US) can be accessed in EDR via:
\\CDSESUB1\EVSPROD\bla761398\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\osteoporosispmo\5354-other-stud-rep\humanfactorstudyinformation\pfs1ml\fksb-r-md-086-02-hf-ue-report-for-fks518-deno-1ml.pdf
The risk management report can be accessed in EDR via:
\\CDSESUB1\EVSPROD\bla761398\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\osteoporosispmo\5354-other-stud-rep\humanfactorstudyinformation\pfs1ml\fksb-ras-md-023-rmr-for-fks518-deno-1ml.pdf

APPENDIX C. INFORMATION REQUESTS ISSUED DURING THE REVIEW

On May 07, 2024, we issued an information request (IR) requesting the Applicant to submit the following:

- (b) (4)
-

On May 09, 2024, the Applicant provided an acceptable response that can be accessed in EDR via: \\CDSESUB1\EVSPROD\bla761398\0004\m5\53-clin-stud-rep\535-rep-effic-safety-stud\osteoporosispmo\5354-other-stud-rep\humanfactorstudyinformation\pfs1ml\response-to-hf-ir-2-received-on-may-07-2024.pdf.

APPENDIX D: LABELS AND LABELING AND PACKAGING

D.1 List of Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[g] along with postmarket medication error experiences with similar products, we reviewed the following FKS518 labeling submitted by Fresenius Kabi, USA, LLC, on March 25, 2024, and July 03, 2024.

Carton labeling and Container label (Image not shown) March 25, 2024	Carton labeling: \\CDSESUB1\EVSPROD\bla761398\0001\m1\us\114-labeling\114a-draft-label\draft-container-labeling-primary-pfs-2-25-ml.pdf Container label: \\CDSESUB1\EVSPROD\bla761398\0001\m1\us\114-labeling\114a-draft-label\draft-container-labeling-primary-pfs-1ml.pdf
Prescribing Information (Image not shown) July 03, 2024	\\CDSESUB1\EVSPROD\bla761398\0009\m1\us\114-labeling\114a-draft-label\draft-labeling-text-uspi-and-medication-guide-1ml-60-mg-pfs.docx

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

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/s/

FLORENCE W MWANGI
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MATTHEW J BARLOW
01/24/2025 05:50:20 PM

ARIANE O CONRAD
01/24/2025 06:12:22 PM

Clinical Inspection Summary

Date	January 17, 2025
From	Ling Yang, M.D., Ph.D., FAAFP Min Lu, M.D., M.P.H., Team Leader Jenn Sellers, M.D., Ph.D., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Olivia Easley, M.D., Clinical Reviewer Shivangi Vachhani, M.D., Clinical Team Leader Julie Van Der Waag, Regulatory Project Manager Division of General Endocrinology (DGE)
BLA #	761398
Applicant	Fresenius Kabi USA, LLC
Drug	FKS518; proposed biosimilar to denosumab
NME (Yes/No)	Yes
Review Priority	Standard
Proposed Indication(s)	Treatment of postmenopausal women with osteoporosis (at high risk for fracture; and treatment of glucocorticoid-induced osteoporosis
Consultation Request Date	May 02, 2024
Summary Goal Date	February 25, 2025
Action Goal Date	March 25, 2025
PDUFA Date	March 25, 2025

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from **Study FKS518-002** entitled "A Double-blind, Randomized, Multicenter, Multiple-dose, 2-arm, Parallel-group Study to Evaluate Efficacy, Pharmacodynamics, Safety, and Immunogenicity of FKS518 – Proposed Biosimilar to Denosumab with Prolia® in Postmenopausal Women with Osteoporosis (LUMIADE-3 Study)" were submitted in this original Biological License Application (BLA) for FKS518; proposed biosimilar to Prolia® and Xgeva® for treatment of postmenopausal women with osteoporosis at high risk for fracture. Two clinical investigators (CIs): Drs. Ewa Krecipro-Nizińska (Site #2305) and Wojciech Pluskiewicz (Site #2306) in Poland were inspected for the submitted study.

The data generated by the CIs and submitted by the sponsor are verifiable. Based on the overall inspection results of these CIs and the regulatory assessments, Study FKS518-002 appears to have been conducted adequately and the clinical data submitted by the sponsor appear acceptable in support of the respective indication.

II. BACKGROUND

Prolia® (denosumab) 60 mg/mL subcutaneous (SC) injection was approved on 06/01/2010 under BLA 125320 for treatment of postmenopausal women with osteoporosis at high risk for fracture. Xgeva® (denosumab) 120 mg/1.7 mL was approved on 11/18/2010 under BLA 125320/07 for the same indication. Fresenius Kabi USA, LLC submitted an original BLA 761398 on 03/26/2024 for FKS518, proposed biosimilar to Prolia® and Xgeva®. Data from Phase 3 Study FKS518-002 were submitted to support the approval.

Study FKS518-002

Study FKS518-002 was a double-blind, randomized, multicenter, multiple-dose, 2-arm, parallel-group study to evaluate the efficacy, pharmacodynamics, safety, and immunogenicity of FKS518 in postmenopausal women with osteoporosis. The product is proposed to be biosimilar to Prolia®.

The primary study objective was to demonstrate equivalent efficacy of the proposed biosimilar denosumab FKS518 to Prolia in postmenopausal women with osteoporosis.

The primary efficacy endpoint was the percent change from baseline in lumbar spine bone mineral density (LS-BMD) by dual-energy X-ray absorptiometry (DXA) at Week 52.

Study Design:

The study consisted of a:

- **Screening Period**: 4 weeks (28 days) prior to randomization.
- **Core Treatment Period**: 52 weeks. Eligible subjects were randomized at a 1:1 ratio to receive SC injection of 60 mg FKS518 or Prolia on Week 0 and Week 26. The randomization was stratified by age (< 65 years or ≥ 65 years) and prior bisphosphonates therapy.
- **Transition Period**: Week 52 - 78. Subjects who were initially randomized to Prolia in the Core Treatment Period were randomly re-assigned at a ratio of 1:1 to either continue receive 60 mg SC injection of Prolia or transition to FKS518. Subjects who were initially randomized to FKS518 continued FKS518 treatment.
- **End of Study (EOS) Visit**: Week 78.
- All subjects received daily supplement of 1000 mg elemental calcium and 400 IU vitamin D.

The study screened 1322 subjects, randomized 553 (277 in FKS518 group and 276 in Prolia group) subjects at 64 study sites in 6 foreign countries: Bulgaria (11), Czech Republic (6), Estonia (4), Georgia (7), Hungary (13) and Poland (23). The first subject was randomized on 06/16/2021 and the last subject's last visit was on 08/07/2023. A total of 501 (252 in FKS518 group and 249 in Prolia group) subjects completed the Core Treatment Period. Of the 249 subjects completed the Core Treatment Period on Prolia, 125 were continued on Prolia and 124 were switched to KFS518. A total of 489 subjects completed the study.

III. RESULTS

1. **Ewa Krecipro-Nizińska, M.D. (Site #2305)**
   Ul. Legnicka 16, Futuremeds
   Wroclaw, Dolnoslaskie
   53-673
   Poland

This CI was inspected on 8/26-30/2024 as a data audit for Study FKS518-002. This was the first FDA inspection of Dr. Krecipro-Nizińska.

For the inspected study, the site screened 97 subjects, enrolled 39 subjects with 36 subjects completed the study. Source records for 23/39 enrolled subjects were reviewed in detail.

The inspection reviewed the study protocol and amendments, Informed Consent Forms (ICFs) and versions, re-consent forms for the transition period, documentation of eligibility criteria and enrollment logs, medical records [including visit data, laboratory tests, physical exam results, adverse events (AEs) and serious AEs (SAEs) reports], investigational product (IP) accountability records, both paper and electronic Case Report Forms (eCRFs) and electronic data capture (EDC) system, protocol deviations and related regulatory documents [e.g., Ethics Committee (EC) approvals and communications, staff trainings, monitoring log, records retention, financial disclosures and delegation of authority].

The submitted data were verifiable with source records at the study site. The primary efficacy endpoint of percent change from baseline in LS-BMD by DXA at Week 52 were central read by Clario (211 Carnegie Center Drive, Princeton, NJ 08450). The inspection reviewed the DXA scan results the site received from the sponsor; and all secondary endpoint data for all reviewed subjects with no discrepancies noted. There were no underreporting of AEs or SAEs.

In general, the inspection verified adequate source data for the inspected studies subjects, with no deficiencies reported.

2. **Wojciech Pluskiewicz, M.D. (Site #2306)**
   Ul. Adama Asnyka 11
   Gabinet Diagnostyki I Leczenia Osteoporozy
   Gliwice, Slaskie
   44-122
   Poland

This CI was inspected on 08/19-23/2024 as a data audit for Study FKS518-002. This was the first FDA inspection of Dr. Pluskiewicz.

For the inspected study, the site screened 66 subjects, enrolled 33 subjects with 30 subjects completed the study. Source records for 12/33 enrolled subjects were reviewed in detail.

The inspection reviewed the study protocol and amendments, ICFs and versions, re-consent forms for the transition period, documentation of eligibility criteria and enrollment logs,

medical records (including visit data, laboratory tests, AEs and SAEs reports), IP accountability records, paper CRFs with eCRFs entries and audit trails, EDC system, protocol deviations and related regulatory documents (e.g., EC approvals and communications, staff trainings, monitoring procedure and logs, records retention, financial disclosures and delegation of authority).

The submitted data were verifiable with source records at the study site. The primary efficacy endpoint data of percent change from baseline in LS-BMD by DXA at Week 52 were central read. The inspection reviewed the DXA scan results the site received from the sponsor; and all secondary endpoint data for all reviewed subjects with no discrepancies noted. There were no underreporting of AEs or SAEs.

In general, the inspection verified adequate source data for the inspected studies subjects, with no significant deficiencies noted.

{See appended electronic signature page}

Ling Yang, 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
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Jenn Sellers, M.D., Ph.D.
Branch Chief
Good Clinical Practice Assessment Branch
Director, Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:
Central Doc. Rm.\BLA 761398
DGE\CDTL\Shivangi Vachhani
DGE\Reviewer\Olivia Easley
DGE\Project Manager\Julie Van Der Vaag
OSI\Director\David Burrow

OSI\Deputy Director\Laurie Muldowney
OSI\DCCE\Division Director\Kassa Ayalew
OSI\DCCE\GCPAB\Branch Chief\Jenn Sellers
OSI\DCCE\GCPAB\Team Leader\Min Lu
OSI\DCCE\GCPAB\Reviewer\Ling Yang
OSI\DCCE\Program Analysts\Yolanda Patague

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/s/

LING YANG
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JENN W SELLERS
01/17/2025 02:34:16 PM

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 19, 2024

TO: Theresa Kehoe, M.D.
Director
Division of General Endocrinology (DGE)
Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN)
Office of New Drugs (OND)

FROM: Xikui Chen, Ph.D.
Pharmacologist
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun Julia Cho, Ph.D.
Director
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Review of Clinical Inspection at MTZ Clinical Research, sp. z o.o., Warsaw, Poland

1. Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged a clinical inspection of study FKS518-001 (BLA 761398, Denosumab injection) conducted at MTZ Clinical Research, sp. z o.o., Warsaw, Poland.

Form FDA 483 was not issued to MTZ Clinical Research, sp. z o.o., Warsaw, Poland. There was one discussion item regarding documentation discrepancies. Based on the inspection finding, I recommend the discussion item has no impact on reliability of the data or human subject protection for study FKS518-001 conducted at the Site.

2. Inspected Study

BLA 761398
Study Number: FKS518-001
Study Title: "A double-blind, randomized, 2-arm, single-dose, parallel-group study in healthy subjects to compare the pharmacokinetics, pharmacodynamics, and immunogenicity of FKS518 – proposed

biosimilar to denosumab with Prolia® (lumiade-1 study)"

Dates of study conduct: May 06, 2021 – September 02, 2022

Clinical site: MTZ Clinical Research, Sp. z.o.o.
Ul. Gładka 22, 02-172, Warszawa, Poland
Principal Investigator: Anna Dryja, MD, MBA

3. Inspectional Findings

3.1 MTZ Clinical Research, sp. z o.o., Warsaw, Poland.

OII investigator Emily A. Baldwin inspected MTZ Clinical Research, sp. z o.o., Warsaw, Poland, from October 14 - 18, 2024.

3.1.1 Previous Inspection

OSIS has no inspection history for this site.

3.1.2 Current Inspection

The current inspection included auditing the following items:
- Case report forms (CRFs)
- Informed consent process
- Protocol deviations
- Institutional Ethics Committee approvals
- Randomization
- Test article accountability, and storage
- Adverse events

3.1.3 Inspection findings

At the conclusion of the inspection, investigator Emily A. Baldwin did not issue Form FDA 483. One discussion item was communicated with management as the following:

Discussion item 1:
The following GCP discrepancies were identified (b) (6)
a. A Screening laboratory report for Subject was signed by Dr. Dryja approximately 10 days before the report was printed. Dr. Dryja signed on (b) (6) was printed on (b) (6)
b. Four (4) discrepancies between source documentation and EDC. During the inspection, Dr. Dryja stated what was written in the source documentation was correct for each.

Table 1.

Subject:	Discrepancy:	Source Documentation	Data Listings/EDC
[redacted] (b) (6)			

OSIS Evaluation 1:

a. The records, provided by Dr. Dryja, Principal Investigator, to OII investigator Emily A. Baldwin on 10/30/2024, showed the screening date for Subject [redacted] (b) (6) Dryja's signature with date of [redacted] (b) (6) laboratory report printout on May 27, 2021, appears to indicate the signature was backdated to the date of the initial lab report of [redacted] (b) (6) demonstrates that the CI's documentation practice is inappropriate. However, I confirmed that there were no discrepancies between the original screening record and the CI-signed document. Thus, the discussion item has no impact on study results and subject safety.

b. I verified discrepancies between the dates of the source documentation and EDC listed in the above Table 1. The discrepancies most likely occurred during the dates transfer from the source documentation to the EDC. Thus, the discussion item has no impact on study results and subject safety.

Draft: XC 12/16/2024, 12/18/2024, 12/19/2024
Edit: MO 12/18/2024; JC 12/18/2024, 12/19/2024

OSIS File: BE 10230

AMS Assignment #: 244604
eNSpect operation ID: 286503

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/s/

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SEONGEUN CHO
12/19/2024 03:14:45 PM

OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS

INTERCENTER CONSULT MEMORANDUM

Instructions | Submission Information

Date	12/4/2024		
To:	ANITA BROWN		
Requesting Center/Office:	CDER/OPQ	**Clinical Review Division:**	N/A-OPQ/OSE led
From	Gang Peng OPEQ/OHT3/DHT3C		
Through (Division) *Optional	Shruti Mistry, Injection Team OPEQ/OHT3/DHT3C		
Subject	BLA 761398 FKS518 ICC2400383		
Recommendation	**Filing Recommendation Date:** Click or tap to enter a date. ☑ CDRH did not provide a Filing Recommendation ☐ Device Constituent Parts of the Combination Product are acceptable for Filing. ☐ Device Constituents Parts of the Combination Product are Acceptable for Filing with Information requests for the 74-Day Letter, See Appendix A ☐ Device Constituents Parts of the Combination Product are Not Acceptable for Filing - See Section 5.4 for Deficiencies		
	Mid-Cycle Recommendation Date: 8/30/2024 ☐ CDRH did not provide a Mid-Cycle Recommendation ☐ CDRH has no approvability issues at this time. ☑ CDRH has additional Information Requests, See Appendix A ☐ CDRH has Major Deficiencies that may present an approvability issue, See Appendix A.		
	Final Recommendation Date: 12/4/2024 ☑ Device Constituent Parts of the Combination Product are Approvable. ☐ Device Constituent Parts of the Combination Product are Approvable with Post-Market Requirements/Commitments, See Section 2.3 ☐ Device Constituent Parts of the Combination Product are Not Approvable - See Section 2.2 for Complete Response Deficiencies		

Digital Signature Concurrence Table

Reviewer	Team Lead (TL)	Division (*Optional)

Remove Buttons

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	BLA 761398
Sponsor	Fresenius Kabi USA, LLC
Drug/Biologic	FKS518
Indications for Use	Proposed biosimilar denosumab Treatment of postmenopausal women with osteoporosis (PMO) at high risk for fracture; treatment of glucocorticoid-induced osteoporosis
Device Constituent	Pre-Filled Syringe with needle safety
Related Files	N/A

Review Team		
Lead Device Reviewer	*Gang Peng*	
Discipline Specific Consults	**Reviewer Name (Center/Office/Division/Branch)**	**CON #**

Important Dates	
Discipline-Specific Review Memos Due	na
Final Lead Device Review Memo Due	12/13/2024(as discussed by email)
Interim Due Dates	**Meeting/Due Date**
Filing	5/1/2024
Mid-Cycle	9/10/2024
BsUFA Original	Mar 25, 2025

2. EXECUTIVE SUMMARY AND RECOMMENDATION

CDRH recommends the combination product is:

☑ Approvable – the device constituent of the combination product is approvable for the proposed indication.

☐ Approvable with PMC or PMR, See Section 2.3

☐ Not Acceptable – the device constituent of the combination product is not approvable for the proposed indication. We have Major Deficiencies to convey, see Section 2.2.

Section	Adequate			Reviewer Notes
	Yes	No	NA	
Device Description	x			
Labeling	x			
Design Controls	x			
Risk Analysis	x			
Design Verification	x			
Consultant Discipline Reviews			x	
Clinical Validation			x	
Human Factors Validation			x	
Facilities & Quality Systems	x			

2.1. Comments to the Review Team

☑ CDRH does not have any further comments to convey to the review team.

☐ CDRH has the following comments to convey to the review team:

2.2. Complete Response Deficiencies

☑ There are no outstanding unresolved information requests, therefore CDRH does not have any outstanding deficiencies.

☐ The following outstanding unresolved information requests should be communicated to the Sponsor as part of the CR Letter:

2.3. Recommended Post-Market Commitments/Requirements

CDRH has Post-Market Commitments or Requirements	☐
CDRH does not have Post-Market Commitments or Requirements	☑

TABLE OF CONTENTS

Update Table of Contents

3. PURPOSE/BACKGROUND

3.1. Scope

Fresenius Kabi USA, LLC is requesting approval of FKS518. The device constituent of the combination product is a Pre-Filled Syringe with needle safety.

CDER/OPQ has requested the following consult for review of the device constituent of the combination product:

This is a proposed denosumab interchangeable biosimilar to the reference products Prolia & Xgeva with the presentation in a pre-filled syringe. The details of the presentations for FKS518 are detailed as follows: -Prefilled Syringe in Safe'n'Sound safety device (60 mg/mL - solution for SC administration)- presentation like US-Prolia. -Vial (120 mg/1.7mL or 70 mg/mL - solution for SC administration)- presentation like USXgeva. -Prefilled Syringe in Safe'n'Sound safety device (120 mg/1.7mL or 70 mg/mL - solution for SC administration)- novel or additional presentation for which the reference product has not been licensed in the US.

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product. This review will cover the following review areas:

Our review will be limited in scope to the Needle Safety Device. PFS performance (e.g. BL/GF and other syringe testing) will be deferred to CDER CMC per the ICCR Agreement Do I Need to Request an Intercenter Consult (i.e., Intercenter Agreements)? (sharepoint.com)

This review will not cover the following review areas:

PFS function unrelating to the needle safety

The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

3.2. Prior Interactions

NA-original BLA

3.2.1. Related Files

NA

3.3. Indications for Use

Combination Product	Indications for Use
FKS518	60g/mL with 1ml long pre-filled syringe with safety device Presentation • Treatment of postmenopausal women with osteoporosis at high risk for fracture • Treatment to increase bone mass in men with osteoporosis at high risk for fracture • Treatment of glucocorticoid-induced osteoporosis in men and women at high risk for • fracture • Treatment to increase bone mass in men at high risk for fracture receiving androgen • deprivation therapy for nonmetastatic prostate cancer • Treatment to increase bone mass in women at high risk for fracture receiving adjuvant • aromatase inhibitor therapy for breast cancer. The frequency of treatment is a single dose, once every six months. Injection with the FKS518 drug product is considered a chronic treatment. 120 mg/1.7mL with 2.25ml pre-filled syringe with safety device Presentation

	The intended medical indication for FKS518 PFS-SNS 2.25 ml is: • Prevention of skeletal-related events in patients with multiple myeloma and patients with • bone metastases from solid tumors • Treatment of adults and skeletally mature adolescents with giant cell tumors of • unresectable bone or where surgical resection is likely to result in severe morbidity. The treatment frequency of use is as follows: • Multiple Myeloma and Bone Metastasis from Solid Tumors: Administer 120 mg every four weeks. Administer calcium and vitamin D as necessary to treat or prevent hypocalcemia. • Giant Cell Tumor of Bone: Administer 120 mg every four weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy. Administer calcium and vitamin D as necessary to treat or prevent hypocalcemia. • Hypercalcemia of Malignancy: Administer 120 mg every four weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy.
Pre-Filled Syringe	Delivery of the Drug Product

3.4. Materials Reviewed

Materials Reviewed	
Sequence	**Module(s)**
\\CDSESUB1\evsprod\BLA761398\0001	m3\32-body-data\32r-reg-info\medicaldevice

4. DEVICE DESCRIPTION

4.1. Device Description

The FKS518 Prefilled Syringe with Safe'n'Sound® Safety System is a single-use, fixed dose (120 mg in 1.7 mL or 60 mg in 1mL), prefilled, and ready-to-use combination product (see Figure 1). The FKS518 Prefilled Syringe with Safety System is composed of a

- prefilled primary container syringe with a staked needle and rigid needle shield (also designated as the "Gray needle cap" in Figure 1 below).
- safety device (off-the-shelf Nemera platform device - Safe'n'Sound)
- attached plunger rod

Figure 1 FKS518 Prefilled Syringe with Safety System

Figure 1 FKS518 Prefilled Syringe with Safety System

Table 2 PFS-SnS Device Assembly Components

Component	Description / Material	Drawing	Picture
Safe 'n' Sound safety device	SnS 2.25mL Staked Safety device (b) (4)	See Figure 2	
Plunger rod	SnS 2.25mL Plunger Rod, white (b) (4)	See Figure 3	

The firm provides LOA to reference **MAF** (b) (4) for Safe'n'Sound®

4.2. Steps for Using the Device

(b) (4)

[redacted]

4.3. Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments The device description is complete, the firm is using an off the shelf device with reference to MAF 2823. The needle safety is well understood and the safe and sound needle safety has been used in other submissions.		
CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

5. FILING REVIEW

CDRH performed Filing Review ☐ **Finalize Filing Review Section**	☐
CDRH was not consulted prior to the Filing Date; therefore CDRH did not perform a Filing Review	☑

6. LABELING

6.1. General Labeling Review

The labeling, including the device constituent labeling, user guides, patient information, prescriber information and all other labeling materials provided for review were reviewed to meet the following general labeling guidelines as appropriate:

General Labeling Review Checklist	Adequate?		
	Yes	No	N/A
Indications for Use or Intended Use; including use environment(s); route(s) of administration for infusion, and treatment population.	x		
Drug name is visible on device constituent and packaging	x		

Device/Combination Product Name and labeling is consistent with the type of device constituent	x		
Prescriptive Statement/Symbol on device constituent	x		
Warnings	x		
Contraindications	x		
Instructions for Use	x		
Final Instructions for Use Validated through Human Factors			x
Electrical Safety Labeling/Symbols			x
EMC Labeling/Symbols			x
Software Version Labeling			x
MRI Labeling/Symbols			x
RF/Wireless Labeling/Symbols			x

Reviewer Comments
Labeling review was restricted to review for the needle safety. As requested in the midcycle deficiency, the firm provided "annex-to-the-response-fksb-sp-md-053-v2-deno-1ml-ifu-us.pdf" which is an updated legible version of the labeling. Overall, the instructions, warnings and indications are appropriate for the needle safety.

6.2. Labeling Review Conclusion

LABELING REVIEW CONCLUSION

Filing Deficiencies:	Mid-Cycle Deficiencies:	Final Deficiencies:
☐ Yes ☐ No ☑ N/A	☑ Yes ☐ No ☐ N/A	☐ Yes ☑ No ☐ N/A

Reviewer Comments
Note that while I will not review the labeling for the PFS, I will review it from a needle safety perspective. The labeling contains information on instructions for use, storage conditions, etc that inform on the needle safety. Overall, the device description is complete for the needle (b) (4)
The general labeling of the device, that are not related to the needle safety will not be captured in this review.

CDRH sent Labeling Deficiencies or Interactive Review Questions to the Sponsor: ☑ Yes ☐ No

	Date Sent: 8/30/2024	Date/Sequence Received: 9/13/2024
Information Request #	(b) (4)	
Sponsor Response	(b) (4)	

	(b) (4)
Reviewer Comments	Reviewer Comment The response is adequate, the updated labeling document is legible and contains information on the needle safety system. Review of the labeling for concerns other than the safety needle safety are deferred to the lead center. (b) (4) (b) (4) The labeling states that storage should be at 2-8C. 8C storage will result in 119.2 days for accelerated aging. It is (b) (4)
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

Add Additional Information Request

☐ **No Additional Information Requests – Finalize Labeling Review Section**

7. DESIGN CONTROL SUMMARY

7.1. Summary of Design Control Activities

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	x		
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)	x		
Mitigations are adequate to reduce risk to health	x		
Version history demonstrates risk management throughout design / development activities	x		
Design Inputs/Outputs	**Yes**	**No**	**N/A**
Design requirements / specifications document present (essential performance requirements included)	x		
Design Verification / Validation Attributes	**Yes**	**No**	**N/A**
Validation of essential requirements covered by clinical and human factors testing	x		
To-be-marketed device was used in the pivotal clinical trial			x
Bioequivalence Study utilized to-be-marketed device			x
Verification methods relevant to specific use conditions as described in design documents and labeling	x		
Device reliability is acceptable to support the indications for use (i.e. emergency use combination product may require separate reliability study)	x		
Traceability demonstrated for specifications to performance data	x		

Reviewer Comments

The firm provided a summary of testing and support for the device within the submission and references MAF (b) (4) Overall, the information is pretty comprehensive for the needle safety. The firm notes a HF study and threshold analysis was provided and used to justify the performance of the combination product, this will be deferred to the lead center.

7.2. Design Inputs and Outputs

(b) (4)

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(b) (4)

Reviewer Comments

The performance specifications are acceptable; they are within normal ranges and the firm has HF studies with the device(defered to lead center)

(b) (4)

Per the scope of this memo, I will only be evaluating the needle safety:
Safety Activation Force
1ml

Table 12 Result of activation and locking in safe mod

(b) (4)	Sample size	Status
	60	Pass
	60	Pass
	60	Pass
	60	Pass
	57	Pass
	60	Pass
	300	Pass
	20	Pass
	20	Pass
	20	Pass

2.25ml

Table 12 Result of activation and locking in safe mod

(b) (4)	Sample size	Status
	60	Pass
	60	Pass
	60	Pass
	60	Pass
	60	Pass
	60	Pass
	300	Pass
	20	Pass
	20	Pass
	20	Pass

Safety Override Force
1ml

Table 13 Result of Override force

(b) (4)	Sample size	(b) (4)	Status
	60		Pass
	60		Pass
	60		Pass
	60		Pass
	60		Pass
	60		Pass
	20		Pass
	20		Pass
	20		Pass

Table 13 Result of Override force

Pre-conditioning	Batch#	Report#	Sample size	Mean	Std. Dev	Status
(b) (4)			60		(b) (4)	Pass
			60			Pass
			60			Pass
			60			Pass
			60			Pass
			300			Pass
			20			Pass
			20			Pass
			20			Pass

From the firm:
A risk-based approach has been used to define the sample size:
(b) (4) units have been selected to ensure (b) (4)% reliability with a (b) (4)% confidence level.
(b) (4) units have been selected to ensure (b) (4)% reliability with a (b) (4)% confidence level.
(b) (4) has been selected to ensure (b) (4)% reliability with a (b) (4)% confidence level.

For shipping:
The firm identifies that the finished pack will be shipped by (b) (4) (b) (4) The simulated shipping mimics the real shipping conditions (b) (4)

Safe n Sound Needle Safety (b) (4) (b) (4)

Table 1 - Summary of Simulated Clinical study for Safe'n'Sound® 1 mL Without Extended Finger Flange (EFF)

Study title	Simulated Clinical Use Testing on a Staked Needle Passive Delivery System
Test device	SAFE 'N' SOUND Staked Passive Delivery System Cone Version (Device A)
Evaluators	15 healthcare professionals and 15 non-healthcare professionals
Study objective	Evaluation of the safety of Device A for the user in the prevention of needlestick injuries.
Primary objectives	- The number of injuries or non-activation of the safety feature reported by the evaluators. o Success is defined as a complete manipulation performed by the evaluator without a needlestick or without contact with the needle and complete activation of the safety feature following injection. o Failure is defined as needlestick injury or non complete activation of the safety feature.
Secondary objectives	- Evaluation of the safety of the device by the evaluators. o safety system being fully activated at the end of injection o cannot be deactivated o remains protective after disposal o no needle accessibility after activation - Evaluation of the ease of use. o no extra step needed o one handed use o reliable performances - Detection of any problems associated with the device. - Evaluation of the type of training needed and the amount of time to adequately train the device users. - Qualitative evaluation of the test device in comparison with 1 comparator device.
Comparator	SAFE 'N' SOUND Staked Passive Delivery System Petal Version (Device B)
Number of devices	- 1 ,000 devices A (675 tested by healthcare professionals (HCP) and 325 by non healthcare professionals (NHCP)) - 45 comparator devices B (30 tested by healthcare professionals (HCP) and 15 by non healthcare professionals (NHCP)
Conclusion	During the simulated clinical trial, no injury occurred on the 1,045 manipulations performed. The objective of 0 injuries is achieved. The analysis of the injury onset and success manipulations showed the following results: - 0 injuries of the SNS Stake Needle Passive Delivery System Cone Version on 325 simulated injections done by NHCP - 0 injuries of the SNS Stake Needle Passive Delivery System Cone Version on 675 simulated injections done by HCP - 0 injuries of the SNS Stake Needle Passive Delivery System Petal Version on 15 simulated injections done by NHCP - 0 injuries of the SNS Stake Needle Passive Delivery System Petal Version on 30 simulated injections done by HCP - On the 1,045 simulated injections done during the study, 0 failures were observed - On the 1,000 simulated injections using the SNS stake needle passive delivery system cone version, 0 failures were observed According to the confidence tables given by the FDA guidance "Medical Devices with Sharps Injury Prevention Features Part 10: Simulated Clinical Use Testing" (page 13}, it is possible to assume a "true" failure rate less than or equal to 0.5% of injury with a confidence level at 99%, when 0 failures were observed in a test run of 1,000 devices. These observations determine that the primary objective of this simulated clinical trial was achieved.
	Concerning the secondary objectives, the evaluators found that the SNS is a safe device, without problem of use, which allowed for them to perform injection using one hand, and does not need extensive training to be operated correctly.

Table 2 - Summary of Simulated Clinical study for Safe'n'Sound® 1 mL With EFF

Study title	Simulated Clinical Use Testing on Safe'n'Sound® 1 mL Staked Passive Delivery System with add-on Extended Finger Flanges
Test device	DEVICE A: Safe'n'Sound® 1 mL Staked Passive Delivery System with add-on Extended Finger Flange
Evaluators	15 healthcare professionals 15 non-healthcare professionals, including 7 impaired (Rheumatoid Arthritis (RA) & Multiple Sclerosis (MS))
Study objective	To estimate the true failure rate of the Safe'n'Sound® 1 mL Staked Passive Delivery system with add-on extended finger flange
Primary objectives	- Failure is defined as needle stick injury (contact with the needle after injection) or non-complete activation of the safety feature. - Success is defined as complete manipulation performed by the evaluator without a needle stick or without contact with the needle after injection and complete activation of the safety feature following injection.
Secondary objectives	Specific secondary objectives are included for this study that cover the following general secondary objectives: - To evaluate the safety of the device based on the evaluators' assessments. - To evaluate various aspects of the ease of use. - To detect any handling questions / issues associated with the device. - To evaluate the current instruction for use and the amount of time to adequately instruct the device users. - To evaluate if usability, holding, gripping, and comfort are improved with the extended finger flange.
Comparator	DEVICE B: Safe'n'Sound® Staked Passive Delivery System – cone version
Number of devices	• 1005 of Device A (test device) (660 tested by healthcare professionals and 345 by non-healthcare professionals) • 180 of Device B (comparator device) (120 tested by healthcare professionals and 60 by non-healthcare professionals)
Conclusion	During the simulated clinical use testing, no injuries occurred with the 1,185 manipulations performed. Failure was defined as needle stick injury (contact with the needle after injection) or non-complete activation of the safety feature. By definition, although the two non-complete activations that occurred in the study were caused by an error in use of the device and were not device malfunctions, these non-complete activations are considered failures. These failures occurred with evaluators who were non-healthcare professionals on their first test/observation for Device A. For non-healthcare professionals, the group in which both of the two failures occurred, the estimated worst case approximation for the true failure rate of Device A is 1.81%. The estimated worst case approximation for the true failure rate of Device A computed for all 1005 Device As used by all 30 evaluators, including healthcare professionals and non-healthcare professionals, is 0.62%. These results indicate that the primary objective of this simulated clinical use testing was achieved for Safe'n'Sound® 1 mL Staked Passive Delivery System with add-on Extended Finger Flanges (Device A). Concerning the secondary objectives, the evaluators reported that Safe'n'Sound® is a safe device that allows for injections to be performed using one hand with no extensive training needed to use the safety device effectively. Overall, evaluators preferred Device A (of the 30 evaluators, 26 preferred Device A over Device B). Results from the evaluator surveys show that holding, gripping, and comfort are improved with the Extended Finger Flanges.

Table 3 - Summary of Simulated Clinical study for Safe'n'Sound® 2.25 mL (with and without EFF)

Study title	Simulated Clinical Use Testing on Safe'n'Sound® 2.25 mL Staked Passive Delivery System with and without Extended Finger Flanges
Test device	Device A (Safe'n'Sound®® 2.25 mL Staked Passive Delivery System WITHOUT Add On Extended Finger Flange) Device B (Safe'n'Sound®® 2.25ml Staked Passive Delivery System WITH Add on Extended Finger Flange)
Evaluators	30 healthcare professionals 30 non-healthcare professionals
Study objective	Evaluation of the safety of Device A for the user in the prevention of needle stick injuries. Evaluation of the safety of Device B for the user in the prevention of needle stick injuries.
Primary objectives	The number of injuries or non-activation of the safety feature for each study device (Device A and Device B) reported by the evaluators. - Success is defined as a complete manipulation performed by the evaluator without a needle stick or without contact with the needle after injection and complete activation of the safety feature following injection. - Failure is defined as needle stick after injection injury or non-complete activation of the safety feature.
Secondary objectives	- Evaluation of the safety of the device by the evaluators. - Evaluation of the ease of use. - Detection of any problems associated with the device. - Evaluation of the grip/ comfort/ holding during injection on a patient with Extended finger flange
Number of devices	• 1005 of Device A (660 tested by healthcare professionals and 345 by non-healthcare professionals) • 1005 of Device B (660 tested by healthcare professionals and 345 by non-healthcare professionals)
Conclusion	Success was defined as a complete manipulation performed by the evaluator without a needle stick or without contact with the needle after injection and complete activation of the safety feature following injection. During the simulated clinical use testing, two needle stick injuries occurred during the 2,010 manipulations performed. Both injuries occurred prior to injection and therefore did not meet the definition of study failure. Three instances of incomplete activation of the safety device were reported and were defined as a study failure; all three instances were not related to device malfunction and were reported by the monitor as being due to user error. Evaluator responses to safety and ease of use questions were favorable. The primary objective of this usability study was to estimate the true failure rate of the Safe'n'Sound® 2.25 ml staked passive delivery system without add-on EFF and estimate the true failure rate of the Safe'n'Sound® 2.25 ml staked passive delivery system with add-on EFF. The study results indicate that with 97.5% confidence, the true failure rate of the Safe'n'Sound® 2.25 ml staked passive delivery system without add-on EFF is no greater than 0.9% (point estimate: 0.3%), and the true failure rate of the Safe'n'Sound® 2.25 ml staked passive delivery system with add-on EFF is no greater than 0.3% (point estimate: 0%). The overall study success rate was 99.85% (2007/2010) with an observed success rate for Device A (syringe without EFF) of 99.7% (1002/1005) and an observed success rate for Device B (syringe with EFF) of 100% (1005/1005). Concerning the secondary objectives, the evaluators reported that Safe'n'Sound® 2.25 ml staked passive delivery system without add-on EFF is a safe device that allows for injections to be performed using one hand with no extensive training needed to use the safety device effectively. Overall, the evaluator surveys show that holding, gripping, and comfort are improved with the Extended Finger Flanges.

Reviewer Comments

The above is a summary of testing for safety activation and override force, the two main specifications we look for in needle safety features.

In response to the midcycle deficiencies, the firm provided a statement and results from the needle safety manufacturer to comply with FDA Guidance "Medical Devices with Sharps Injury Prevention Features" as well as ISO 23908:2011 "Sharps injury protection — Requirements and test methods — Sharps protection features for single-use hypodermic needles, introducers for catheters and needles used for blood sampling". The studies were conducted with 15 healthcare professionals and 15 non-healthcare professionals on 1000 devices. Overall, the study met the objectives of demonstrating the safety of the needle safety device. Although some failures did occur, this was due to user or happened prior to the needle safety activation and not attributed to the needle safety itself. Note that the safe and sound needle safety has been used in other submissions as well.

The firm also provided justification for the choice of accelerated aging testing temperature as well(testing using 5C storage condition) and the use of n=57 for needle safety activation. The justifications are adequate(see below interactions) and there are no additional concerns on EPRs.

7.3. Applicable Standards and Guidance Documents

Standard or Guidance	Conformance (Y/N/NA)
Standard Practice for Performance Testing of Shipping Containers and Systems; ASTM D4169-09	Y
Guidance for Industry and FDA Staff – Medical Devices with Sharps Injury Prevention Features (2005)	Y
ISO 23908:2011 Sharps Injury Protection – Requirements and test methods – Sharps protection features for single-use hypodermic needles, introducers for catheters and needles used for blood sampling	Y

7.4. Design Control Review Conclusion

DESIGN CONTROL REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☑ Yes ☐ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments The firm has identified the relevant standards for the needle safety and stated that they are applicable/conforming. Note that they state conformance to other standards as well but I've only kept the ones relevant to the needle safety.		
CDRH sent Design Control Deficiencies or Interactive Review Questions to the Sponsor: ☑ Yes ☐ No		

	Date Sent: 8/30/2024	**Date/Sequence Received:** 9/13/2024
Information Request #	(b) (4)	

Sponsor Response	Section R.2.3 Medical Device Overview has been updated to include the statement and results from the Safe and Sound® device manufacturer (Nemera) claiming compliance with FDA Guidance "Medical Devices with Sharps Injury Prevention Features" as well as ISO 23908:2011 "Sharps injury protection — Requirements and test methods — Sharps protection features for single-use hypodermic needles, introducers for catheters and needles used for blood sampling". Successful simulated clinical use tests were conducted by the manufacturer (Nemera) of the safety system devices (Safe'n'Sound Staked Passive Delivery System) for both presentations (1mL and 2.25mL) to comply with the FDA Guidance "Medical Devices with Sharps Injury Prevention Features" and to ISO 23908:2011. The studies were conducted with 15 healthcare professionals and 15 non-healthcare professionals on 1000 devices.
Reviewer Comments	The response is adequate, the firm performed simulated clinical testing with the configurations of the safe and sound. The studies were conducted with 15 healthcare professionals and 15 non-healthcare professionals on 1000 devices. Overall, the study met the objectives of demonstrating the safety of the needle safety device. Although some failures did occur, this was due to user or happened prior to the needle safety activation and not attributed to the needle safety itself. Note that the safe and sound needle safety has been used in other submissions as well.
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

	Date Sent: 8/30/2024	**Date/Sequence Received:** 8/13/2024
Information Request #	(b) (4)	
Sponsor Response	The FKS518 finished combination products (both 1mL and 2.25mL) is intended to be stored in its original carton between 2°C to 8°C and 5°C (b) (4)	

	(b) (4)
Reviewer Comments	The response is inadequate. It is unclear why choosing the middle value for storage is appropriate rather than choosing the worst case(storage is set at 2 to 8C). I do not believe this is appropriate (b) (4) (b) (4). The firm should test with the worst case storage temperature.
Response Adequate:	☐ **Yes** ☑ **No, See IR # Sent on** Click or tap to enter a date.

Follow-On Deficiency	**Date Sent: 11/5/2024**	**Date/Sequence Received: 11/7/2024**
Information Request #	(b) (4)	
Sponsor Response	(b) (4)	

	(b) (4) [redacted]
Reviewer Comments	The response is adequate. I spoke with the lead center on this concern. For the lead center and drug product quality, the statement of storage at 5°C ± 3°C or 2°C to 8°C are identical. (b) (4) [redacted]

Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

	Date Sent: **8/30/2024**	**Date/Sequence Received:** **9/13/2024**
Information Request #	(b) (4)	
Sponsor Response	(b) (4)	

(b) (4)

(b) (4)

(b) (4)

In conclusion, the Applicant considers that the overall data available on the Safe'n'Sound's safety device is robust and deems that the essential performance requirement related to the automatic activation and locking of the safety device is verified against the defined confidence and reliability intervals, and that the proposed combination product can be used safely by the intended users.

Reviewer Comments	I realized that we mistakenly stated that (b) (4) confidence, reliability is adequate; usually (b) (4) confidence, reliability is necessary for needle safety features. After chatting with the AD, it was decided that in order to be least burdensome and considering a risk based approach, (b) (4) may be appropriate. This is because the needle safety system (safe and sound) has been used in many other submissions without issues and we are not aware of any signals related to the safe and sound needle safety. The clinical study provided by the firm also did not reveal any issues with the safe and sound safety system itself. Therefore, considering the above information, risks are adequately mitigated to accept (b) (4) % confidence, reliability even though (b) (4) is ideal. For the n-57, The firm states that the failures that occurred were not due to the safety mechanism but rather to the assembly process. In the root cause, the non activated devices were observed to have bending of tabs where the needle safety and syringe are joined. While the failure may not be a failure of the needle safety, this does raise concern on the manufacturing of the finished device and why the joining of the needle safety and PFS resulted in bending of tabs on the safety, leading to improper activation. It is important to note, as the firm points out, the safe and sound needle safety has been used in other applications and devices. However, this only points to support the safe and sound needle safety system rather than the combination of the entire product including the PFS. There may be issues with the manufacturing process that introduces failures due to the way the needle safety and PFS are joined.
Response Adequate:	☐ **Yes** ☑ **No, See IR # Sent on** Click or tap to enter a date.

Follow-On Deficiency	**Date Sent:** 11/5/2024	**Date/Sequence Received:** 11/7/2024
Information Request #	(b) (4)	

	(b) (4)
Sponsor Response	(b) (4)

	(b) (4)
Reviewer Comments	The response is adequate. (b) (4) (b) (4)

	(b) (4)
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

Add Additional Information Request

☐ **No Additional Information Requests – Finalize Design Control Review Section**

8. DESIGN VERIFICATION REVIEW

8.1. Performance/Engineering Verification

8.1.1. Essential Performance Requirement Evaluation

Note only elements relevant to needle safety will be captured

Essential Performance Requirement (Design Input)	Specification (Design Output)	Verification Method Acceptable (Y/N)	Validation (Y/N)	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)
Safety System Activation	Device Activate and lock in safe mode	Y	Y	Y	Y
Safety System Activation Override Force	≥ (b)(4) N	Y	Y	Y	Y

Reviewer Comment

The only relevant specifications are the needle safety activation and override. The specification set are reasonable; we commonly see the >(b)(4) N value for override. The firm has performed HF and threshold analysis which will be deferred to the lead center to review. The specifications are evaluated after conditioning, shipping and aging.

8.1.2. Verification of Design Inputs Evaluation

Design Input	Design Output	Verification Method	Results/Deviations	Adequately Verified (Y/N)	Validated through Clinical, Human Factors or Other	Adequately Validated (Y/N)
Safety System Activation	Device Activate and lock in safe mode	FKSB 165097 TR2-V1 The activation of the safety system is tested as it activates after injectino	Pass	Y	Y	Y
Safety System Activation Override Force	≥ (b)(4) N	FKSB 165097 TR2-V1 The override force was tested subject to tensile force	Pass	Y	Y	Y

Reviewer Comment

The only relevant specifications are the needle safety activation and override. The specification set are reasonable; we commonly see the >(b)(4) N value for override. The firm has performed HF and threshold analysis which will be deferred to the lead center to review. The specifications are evaluated after conditioning, shipping and aging.

8.1.3. Evaluation of Test Methods

Title:	FKSB 165097 TR2-V1
Scope/Objective & Acceptance Criteria:	Test of safety feature activation under standard and conditioned environment. Acceptance Criteria: safety feature activates upon injection completion

Methods	The device contains a needle safety feature(spring powered) which retracts the needle once the user is no longer depressing the plunger/needle. The test evaluates whether the needle is successfully retracted into the device upon release of the plunger.
Results:	Pass
Conclusions/ Reviewer Comments:	The firm tested the activation of the safety feature. The device(1 and 2.25ml) met the criteria of activating after use. The test is passing and the safety activation for the safety feature is verified.
Acceptable:	☒Yes ☐No

Title:	FKSB 165097 TR2-V1
Scope/Objective & Acceptance Criteria:	Test of override force(>(b) (4)N) under standard and conditioned environment. Acceptance Criteria>(b) (4)N for override
Methods	An upper fixture connected to the force sensor pressed the needle cover down until it overrides the safety feature. The maximum force at a test speed of (b) (4) mm/minute was recorded as the result.
Results:	Pass
Conclusions/ Reviewer Comments:	The firm tested the force needed to override the safety feature. The device(1 and 2.25ml) met the criteria of >(b) (4)N of force. The test is passing and the override force specification for the safety feature is verified.
Acceptable:	☒Yes ☐No

Reviewer Comment

As this memo is limited to review of the needle safety, review of the needle safety activation and override are the only relevant performance specifications. The firm tested both specifications after conditioning and aged to meet the specification. Testing results and methods are acceptable.

8.2. Design Verification Review Conclusion

DESIGN VERIFICATION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments The verification of the needle safety EPRs is complete. Based on the totality of evidence present, I do not anticipate concerns with the safety/performance of the Safe n Sound needle safety system.		
CDRH sent Design Verification Deficiency or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

8.3. Discipline Specific Sub-Consulted Review Summary

☑ No Additional Discipline Specific Sub-Consults were requested

☐ The following additional Discipline Specific Sub-Consults were requested:

9. CLINICAL VALIDATION REVIEW

9.1. Review of Clinical Studies Clinical Studies

☑ There is no device related clinical studies for review
☐ There are clinical studies for review

10. HUMAN FACTORS VALIDATION REVIEW

CDRH Human Factors Review conducted	☐
Human Factors deferred to DMEPA	☑

11.FACILITIES & QUALITY SYSTEMS

11.1. Facility Inspection Report Review

CDRH Facilities Inspection Review conducted	☐
CDRH Facilities Inspection Review was not conducted	☑

11.2. Quality Systems Documentation Review

CDRH Quality Systems Documentation Review conducted	☐
CDRH Quality Systems Documentation Review was not conducted	☑

11.3. 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 EPRs	The firm will have in process controls for the purchasing of the safe n sound along with implementing in process controls for inspection of produced batches	Y

Reviewer Comments

The firm states that there will be in process controls to inspect the finished PFS-NSD to evaluate the function/safety of the product. Note that the needle safety is a product that has been used in other submissions(some of which are also belonging to this firm) and the firm will have incoming controls for the NSD.

Control Strategy Conclusion		
The Sponsor provided adequate information to support the manufacturing control activities for the essential performance requirements of the combination product.	☒Yes	☐No

11.4. Facilities & Quality Systems Review Conclusion

FACILITIES & QUALITY SYSTEMS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments Facilities review not needed as this review focuses on needle safety review; there are no facilities/quality system concerns.		
CDRH sent Facilities & QS Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

<<END OF REVIEW>>

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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: 9/3/2024

TO: Division of General Endocrinology (DGE)
Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN)

FROM: Office of Study Integrity and Surveillance (OSIS)

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

RE: BLA 761398

The Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not needed for the site listed below. The rationale for this decision is noted below.

Rationale

(b) (4): OSIS conducted a Remote Regulatory Assessment (RRA) for the analytical site in (b) (4). The RRA was conducted under the following submission: NDA (b) (4).

OSIS concluded that data from the reviewed studies were reliable.

Site

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	

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/

FELECIA P HAGOOD
09/16/2024 02:32:54 PM