CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761392Orig1s000
761392Orig2s000

OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED 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:	February 10, 2025
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	BLA 761392
Product Name, Dosage Form, and Strength:	Ospomyv (denosumab-dssb) injection, 60 mg/mL
Applicant Name:	Samsung Bioepis Co., Ltd.
FDA Received Date:	February 7, 2025
TTT ID #:	2024-8268-3
DMEPA 1 Safety Evaluator:	Amy J. Bao, PharmD, MPH
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 PURPOSE OF MEMORANDUM

Samsung Bioepis Co., Ltd. submitted revised carton labeling received on February 7, 2025 for Ospomyv. The Division of General Endocrinology (DGE) requested that we review the revised carton labeling for Ospomyv (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made to align carton labeling to the "Ospomyv should be administered by a healthcare provider" statement that appears in Section 2.3 of the Prescribing Information.

2 CONCLUSION

Samsung Bioepis Co., Ltd. implemented all of our recommendations and we have no additional recommendations at this time.

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AMY J BAO
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YEVGENIYA M KOGAN
02/10/2025 12:40:22 PM

MEMORANDUM
REVIEW OF REVISED 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:	February 10, 2025
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	BLA 761392
Product Name, Dosage Form, and Strength:	Xbryk (denosumab-dssb) injection, 120 mg/1.7 mL (70 mg/mL)
Applicant Name:	Samsung Bioepis Co., Ltd.
FDA Received Date:	February 7, 2025
TTT ID #:	2024-8282-3
DMEPA 1 Safety Evaluator:	Amy J. Bao, PharmD, MPH
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 PURPOSE OF MEMORANDUM

Samsung Bioepis Co., Ltd. submitted revised carton labeling received on February 7, 2025 for Xbryk. The Division of General Endocrinology (DGE) requested that we review the revised carton labeling for Xbryk (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made to align carton labeling to the "Xbryk should be administered by a healthcare provider" statement that appears in Section 2.1 of the Prescribing Information.

2 CONCLUSION

Samsung Bioepis Co., Ltd. implemented all of our recommendations and we have no additional recommendations at this time.

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YEVGENIYA M KOGAN
02/10/2025 12:43:02 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)

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Date of This Review:	January 27, 2025
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	BLA 761392
Product Name, Dosage Form, and Strength:	Ospomyv (denosumab-dssb) injection, 60 mg/mL
Applicant Name:	Samsung Bioepis Co., Ltd.
FDA Received Date:	January 21, 2025
TTT ID #:	2024-8268-2
DMEPA 1 Safety Evaluator:	Amy J. Bao, PharmD, MPH
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 PURPOSE OF MEMORANDUM

Samsung Bioepis Co., Ltd. submitted revised container labels and carton labeling received on January 21, 2025 for Ospomyv. The Division of General Endocrinology (DGE) requested that we review the revised container labels and carton labeling for Ospomyv (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

Samsung Bioepis Co., Ltd. implemented all of our recommendations and we have no additional recommendations at this time.

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

[a] Bao, A. Review of Revised Label and Labeling for Ospomyv (BLA 761392). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 Dec 18. TTT ID: 2024-8268-1.

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AMY J BAO
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YEVGENIYA M KOGAN
01/27/2025 03:18:24 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)

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Date of This Review:	January 27, 2025
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	BLA 761392
Product Name, Dosage Form, and Strength:	Xbryk (denosumab-dssb) injection, 120 mg/1.7 mL (70 mg/mL)
Applicant Name:	Samsung Bioepis Co., Ltd.
FDA Received Date:	January 21, 2025
TTT ID #:	2024-8282-2
DMEPA 1 Safety Evaluator:	Amy J. Bao, PharmD, MPH
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 PURPOSE OF MEMORANDUM

Samsung Bioepis Co., Ltd. submitted revised container labels and carton labeling received on January 21, 2025 for Xbryk. The Division of General Endocrinology (DGE) requested that we review the revised container labels and carton labeling for Xbryk (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

Samsung Bioepis Co., Ltd. implemented all of our recommendations and we have no additional recommendations at this time.

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

[a] Bao, A. Review of Revised Label and Labeling for Xbryk (BLA 761392). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 Dec 18. TTT ID: 2024-8282-1.

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AMY J BAO
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YEVGENIYA M KOGAN
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M E M O R A N D U M

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

DATE: December 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: Makini Cobourne-Duval, Ph.D.
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
DGDSI
OSIS

SUBJECT: Review of Clinical Inspections of Biotrial Inc., Newark, New Jersey, and Biotrial Rennes, Rennes Cedex, France

1. Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged clinical inspections of study SB16-1001 under BLA 761392 cross-referenced with IND 141802 conducted at Biotrial Inc., Newark, New Jersey, and Biotrial Rennes, Rennes Cedex, France.

No Form FDA 483 was issued at the inspection close-out for either site. However, there were four discussion items addressed at the Biotrial Inc. (New Jersey) inspection close-out, and one discussion addressed at the Biotrial Rennes (France) inspection close out. Based on the inspection findings, there are no identified concerns for Biotrial Rennes regarding reliability of the data or human subject protection for inspected study SB16-1001. However, there was one identified concern regarding Subject (b) (6) at Biotrial Inc., which OSIS defers to the review division to determine whether the inclusion of the data from this subject impacts the reliability of the data.

2. Inspected Study:

BLA 761392

Study Number: SB16-1001
Study Title: "A Randomised, Double-blind, Three-arm, Parallel Group, Single-dose Study to Compare the Pharmacokinetics, Pharmacodynamics, Safety, Tolerability, and Immunogenicity of Denosumab (SB16, EU Sourced Prolia, and US Sourced Prolia) in Healthy Male Subjects"
Dates of study conduct: 10/21/2020 – 11/9/2022

Clinical site: Biotrial Inc.
130 Norfolk Street
Newark, New Jersey 07103-3225

Clinical site: Biotrial Rennes
7 rue Jean-Louis Bertrand
35042 Rennes Cedex, Ille-et-Vilaine
Region of Brittany, France

3. Inspectional Findings

Biotrial Inc., Newark, NJ

OII investigators Jay B. Shah and Michael Serrano inspected Biotrial Inc., 130 Norfolk Street, Newark, NJ, from October 28 – November 5, 2024.

3.1 Previous Inspection

This was the first OSIS inspection of Grissel Flores, APN and Biotrial Inc. under the BA/BE program.

3.2 Current Inspection

The CI responsibility was transferred in June 2022 from the study's initial clinical investigator, Michael Dubrow, D.O., upon his resignation to Grissel Flores, APN, who previously served as the study's sub-investigator.

The current inspection included auditing the following items:

-Electronic case report forms (eCRFs)
-Informed consent process
-Protocol deviation detection and reporting
-Financial disclosure forms

-Personnel training
-Institutional review board (IRB) approvals
-Investigational product (IP) administration and accountability
-Randomization
-Adverse events
-Relevant clinical facilities and equipment

3.3 Inspection findings

At the conclusion of the inspection, investigators Jay B. Shah and Michael Serrano did not issue Form FDA 483 to the clinical site. However, there were four discussion items addressed at the inspection close-out. The discussion items, the firm's response per the EIR, and my evaluation are presented below.

3.3.2. Discussion Items

Discussion item 1:
The site did not report the occurrence of a protocol deviation for a subject:

- Subject (b) (6) was not fasted the minimum 8 hours prior to the Day 43 fasting PK blood sample collection.

OSIS Evaluation:
Per protocol, the Day 43 blood sampling should be collect following a fast of at least 8 hours (1008 hours after IP administration). After my review of the provided exhibits, I confirmed that this incident cited in Discussion Item 1 was a protocol deviation. This protocol deviation for Subject (b) (6) was not reported to the sponsor. When conducting a study, good clinical practice requires that a site report all protocol deviations documented in the study source records. The firm did not meet this standard in this case. However, per the EIR, besides this protocol deviation, all other protocol deviations were appropriately reported to the sponsor and reflected in the data listings provided to the FDA. Therefore, I conclude that this incident was isolated and defer to the review division to determine its impact on data reliability.

Firm's Response:
No specific response to any of the discussion items was provided. Per the EIR, the general response to all four of the discussion items was provided: *The study team acknowledged and understood the discussion items and stated that they will be diligent about avoiding such errors in the future.*

Discussion item 2:
There was an inaccuracy recorded in the paper case report form for Subject (b) (6) regarding whether the subject experienced any new adverse events since the last visit.

OSIS Evaluation:
A CI at the clinical site should accurately document the occurrence of adverse events when conducting a study. There was a discrepant documentation of the AE experienced by Subject (b) (6) when comparing the paper case report form to the Adverse Events/Concomitant Medication source record. However, I confirmed that the AE documented in the Adverse Events/Concomitant Medication source record was appropriately reported to the Sponsor and matched the AE listing (Listing 16.2.7-1.1) provided to the Agency. Therefore, I conclude that this discussion item has no impact on the reliability of the data.

Firm's Response:
See firm's response to Discussion Item 1 above.

Discussion item 3:
There were discrepancies in the eCRFs compared to the paper-based study source records for three subjects:

- Subject (b) (6): discrepancy in the time recorded of when an injection site reaction check was performed by the study nurse i.e., (b) (6) vs. (b) (6).
- Subject (b) (6): discrepancy in the fasting state prior to Day 43 fasting PK blood collection i.e., fasting vs. not fasting.
- Subject (b) (6): discrepancy in the time recorded of when the vital signs were documented i.e., (b) (6) vs. (b) (6).

OSIS Evaluation:
When conducting a study, a CI at the clinical site should report accurate details that were documented in the study source records. I verified the discrepancies cited in Discussion Item 3. However, the time discrepancies cited for an injection site reaction check and vital signs check for Subjects (b) (6), respectively, are relatively minor (5 minutes) and within the context of the study have no impact on the reliability of the data. The discrepancy cited for Subject (b) (6) is related to Discussion Item 1 and has been addressed in that corresponding evaluation.

Firm's Response:
See firm's response to Discussion Item 1 above.

Discussion item 4:
The site did not record progress notes to provide detailed information related to the adverse events of multiple subjects:

- Subject (b) (6) tinnitus ((b) (6))
- Subject elevated CPK levels ((b) (6))
- Subject light-headedness ((b) (6))
- Subject chills ((b) (6))
- Subject intermittent toothache ((b) (6))

OSIS Evaluation:
Per protocol, "When reporting an AE, a diagnosis (when possible and appropriate) rather than each individual sign and symptom should be reported." There is no requirement in the study protocol or in the regulations that the firm record detailed progress notes for each adverse event. Hence, this discussion item is not a protocol or regulatory violation. For each of the cited subjects, the firm appropriately reported the adverse event diagnosis, start date and time, end date and time, severity, relationship to IP, and any corrective treatment/procedure. Therefore, I conclude that this discussion item has no impact on data reliability or subject safety.

Firm's Response:
See firm's response to Discussion Item 1 above.

Biotrial Rennes, Rennes-Cedex, France

OII investigator Denise L. Burosh inspected Biotrial Rennes, 7 rue Jean-Louis Bertrand, Rennes-Cedex, France from September 2-6, 2024.

3.1 Previous Inspection

This was the first OSIS inspection of Clinical Investigator Dr. Hakim Charfi at Biotrail Rennes under the BA/BE program. The previous OSIS inspection of Biotrial Rennes was conducted from February 21-25, 2022. At the conclusion of the inspection no Form FDA 483 was issued. However, there was one discussion item for non-contemporaneous source documentation of adverse events for 8 of 16 subjects. The final classification was NAI.

3.2 Current Inspection

The current inspection included auditing the following items:

-Case report forms (CRFs)
-Subject source records

-Informed consent process
-Protocol adherence
-Institutional review board approvals and correspondence
-Financial disclosure reports
-Monitoring reports
-Investigational product (IP) accountability and dispensing records
-Randomization
-Adverse event reporting
-Protocol deviation reporting

3.3 Inspection findings

At the conclusion of the inspection, investigator Denise L. Burosh did not issue Form FDA 483 to the clinical site. However, there was one discussion item addressed at the inspection close-out. The discussion item, the firm's response per the EIR, and my evaluation are presented below.

3.3.1. Discussion Item

Discussion item 1:
The site did not retain representative reserve samples from the second and third shipments of IPs received and used during the study.

OSIS Evaluation:
Per FDA Guidance for Industry "Questions and Answers on Biosimilar Development and the BPCI Act" (September 2021), the Agency recommends that the *sponsor* of a proposed biosimilar product retain reserve samples for at least 5 years following the date of completion of a comparative clinical PK and/or PD study of the reference product and the proposed biosimilar product. There is no regulatory requirement that the clinical site or CI maintain reserves for proposed biosimilar products. In addition, this discussion item is purely a recommendation of OII investigator rather than an observation of an objectionable condition regarding the retention of reserves. I conclude that this discussion item has no impact on data reliability.

Firm's Response:
Per the EIR, management stated that they understood and promised to follow their procedures and contract requirements with the sponsor.

Makini Cobourne-Duval, Ph.D.
Pharmacologist

Draft: MCD 12/2/2024, 12/3/2024, 12/17/2024, 12/18/2024, 12/19/2024
Edit: MO 12/19/2024; JC 12/19/2024

OSIS File #: BE 10205

eNSpect Assignment ID: 243672
eNSpect OpID: 285228 (Biotrial, Inc.)
285195 (Biotrial Rennes)

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/s/

MAKINI COBOURNE-DUVAL
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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:	December 18, 2024
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	BLA 761392
Product Name, Dosage Form, and Strength:	Ospomyv (denosumab-dssb) injection, 60 mg/mL
Applicant Name:	Samsung Bioepis Co., Ltd.
FDA Received Date:	December 2, 2024
TTT ID #:	2024-8268-1
DMEPA 1 Safety Evaluator:	Amy J. Bao, PharmD, MPH
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 PURPOSE OF MEMORANDUM

Samsung Bioepis Co., Ltd. submitted revised container labels and carton labeling received on December 2, 2024 for Ospomyv. The Division of General Endocrinology (DGE) requested that we review the revised container labels and carton labeling for Ospomyv (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. The nonproprietary name suffix is not presented in an appropriate font style, the proprietary name, nonproprietary name, and dosage form lack prominence on the principal display panel, and the location of the lot and expiration placeholders should be adjusted.

3 RECOMMENDATIONS FOR SAMSUNG BIOEPIS CO., LTD.

A. General Comments (Container Labels and Carton Labeling)

1. Please refer to the General Advice Letter, dated December 17, 2024, which notified you of the nonproprietary name found conditionally acceptable for your proposed product. Should your BLA be approved during this review cycle, "denosumab-dssb" will be the proper name designated in the license. Revise the nonproprietary name on all labeling to incorporate the FDA-designated nonproprietary name suffix, "-dssb", appended to the core name, "denosumab", so that the proper name appears as "denosumab-dssb" throughout the labeling. We note the nonproprietary name suffix on the unbranded labeling appears in all caps and a different font size compared to the core name. Please ensure that the nonproprietary name suffix appears in lowercase letters and is the same font size as the core name. See *Draft Guidance for Industry: Nonproprietary Naming of Biological Products: Update (March 2019).*

B. Container Labels

1. We recommend unbolding "For subcutaneous use only" and "Mfd by:" so as to not compete in prominence with the proprietary name and nonproprietary name.
2. We note that the lot number and expiration date placeholders are currently both printed under "LOT". Ensure the "LOT" and "EXP" and the variable text placeholders for the lot number and expiration date will be printed such that they are labeled appropriately.

[a] Bao, A. Label and Labeling Review for Ospomyv (BLA 761392). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 Dec 13. TTT ID: 2024-8268.

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

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/s/

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YEVGENIYA M KOGAN
12/18/2024 02:31:03 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)
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Date of This Review:	December 18, 2024
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	BLA 761392
Product Name, Dosage Form, and Strength:	Xbryk (denosumab-dssb) injection, 120 mg/1.7 mL (70 mg/mL)
Applicant Name:	Samsung Bioepis Co., Ltd.
FDA Received Date:	December 2, 2024
TTT ID #:	2024-8282-1
DMEPA 1 Safety Evaluator:	Amy J. Bao, PharmD, MPH
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 PURPOSE OF MEMORANDUM

Samsung Bioepis Co., Ltd. submitted revised container labels and carton labeling received on December 2, 2024 for Xbryk. The Division of General Endocrinology (DGE) requested that we review the revised container labels and carton labeling for Xbryk (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. The nonproprietary name suffix is not presented in an appropriate font style, the dosage form lacks prominence on the principal display panel, and there is a typo in the content statement.

3 RECOMMENDATIONS FOR SAMSUNG BIOEPIS CO., LTD.

A. General Comments (Container Labels and Carton Labeling)

1. Please refer to the General Advice Letter, dated December 17, 2024, which notified you of the nonproprietary name found conditionally acceptable for your proposed product. Should your BLA be approved during this review cycle, "denosumab-dssb" will be the proper name designated in the license. Revise the nonproprietary name on all labeling to incorporate the FDA-designated nonproprietary name suffix, "-dssb", appended to the core name, "denosumab", so that the proper name appears as "denosumab-dssb" throughout the labeling. We note the nonproprietary name suffix on the unbranded labeling appears in all caps and a different font size compared to the core name. Please ensure that the nonproprietary name suffix appears in lowercase letters and is the same font size as the core name. See *Draft Guidance for Industry: Nonproprietary Naming of Biological Products: Update (March 2019).*

B. Carton Labeling

1. Please correct a misspelling in the content statement and change "desnosumab-xxxx" to "denosumab-dssb".

[a] Bao, A. Label and Labeling Review for Xbryk (BLA 761392). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 Dec 13. TTT ID: 2024-8282.

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/s/

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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:	December 13, 2024
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	BLA 761392
Product Name, Dosage Form, and Strength:	Ospomyv (denosumab-xxxx)[a] injection, 60 mg/mL
Product Type:	Combination Product (Biologic-Device)
Rx or OTC:	Prescription (Rx)
Applicant Name:	Samsung Bioepis Co., Ltd.
FDA Received Date:	February 12, 2024, September 10, 2024, and November 13, 2024
TTT ID #:	2024-8268
DMEPA 1 Safety Evaluator:	Amy J. Bao, PharmD, MPH
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

[a] The non-proprietary name suffix for this product has not yet been determined; therefore, the placeholder "denosumab-xxxx" is used throughout this review to refer to the non-proprietary name and suffix for this product.

1 INTRODUCTION

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

1.1 BACKGROUND

Ospomyv (denosumab-xxxx) 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 761392.

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 unbranded Ospomyv Prescribing Information (PI) and Medication Guide (MG) and determined that they are acceptable from a medication error perspective.

However, the proposed branded Ospomyv Prescribing Information (PI) and Medication Guide (MG), container labels, and carton labeling, and the proposed unbranded Ospomyv 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 Samsung Bioepis Co., Ltd. in Section 5.

4 RECOMMENDATIONS FOR THE DIVISION OF GENERAL ENDOCRINOLOGY (DGE)

A. Branded Prescribing Information

1. As currently presented, the proprietary name is denoted by the placeholder "SB16 60 mg PFS". We are unable to assess the prominence and readability of the intended presentation of the proprietary name. We reference our October 23, 2024 Proprietary Name Request Conditionally Acceptable letter informing you that the proprietary name, Ospomyv, was found conditionally acceptable. We recommend replacing the placeholder "SB16 60 mg PFS" with the conditionally acceptable proprietary name, Ospomyv.

B. Branded Medication Guide

1. As currently presented, the proprietary name is denoted by the placeholders "SB16" and "SB16 60 mg PFS". We are unable to assess the prominence and readability of the intended presentation of the proprietary name. We reference our October 23, 2024 Proprietary Name Request Conditionally Acceptable letter informing you that the proprietary name, Ospomyv, was found conditionally acceptable. We recommend replacing the placeholders "SB16" and "SB16 60 mg PFS" with the conditionally acceptable proprietary name, Ospomyv.

5 RECOMMENDATIONS FOR SAMSUNG BIOEPIS CO., LTD.

A. General Comments (Container Labels and Carton Labeling)

1. As currently presented, the proprietary name is denoted by the placeholders "SB16" and "SB16 PFS". We are unable to assess the prominence and readability of the intended presentation of the proprietary name. We reference our October 23, 2024 Proprietary Name Request Conditionally Acceptable letter informing you that the proprietary name, Ospomyv, was found conditionally acceptable. We recommend replacing the placeholders "SB16" and "SB16 PFS" with the conditionally acceptable proprietary name, Ospomyv, 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. The strength is not clearly differentiated due to the similarity between the (b) (4) color which overlaps with the font color used for the nonproprietary name. Color differentiation is most effective when the color used has no association with a particular feature. We recommend revising the color of the nonproprietary name (consider a black font color to align with the dosage form font color) or the color of the box surrounding the strength, such that the strength and the nonproprietary name appear in their own unique colors that do not overlap.
3. As currently presented, the format for the expiration date is not defined. We are unable to assess the proposed expiration date format from a medication safety perspective. To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend identifying the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or 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)*.
4. For the unbranded container labels and carton labeling, we note the biological suffix "-XXXX" appears on a separate line from "Denosumab". We recommend keeping the core name and the suffix on the same line of text in order to prevent any misinterpretation of the full nonproprietary name.

B. Container Labels

1. It is unclear which direction the container label will wrap around the body of the prefilled syringe. Please confirm the linear barcode is oriented on the container

label such that it is not distorted or obstructed by the container curvature (i.e., following the length of the syringe body) in order to improve scannability.

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. The Medication Guide (MG) statement is located on a side panel. Per 21 CFR 208.24(d), the label of each container or package, where the container label is too small, of drug product for which a Medication Guide is required under this part shall instruct the authorized dispenser to provide a Medication Guide to each patient to whom the drug product is dispensed, and shall state how the Medication Guide is provided. These statements shall appear on the label in a prominent and conspicuous manner. Ensure the Medication Guide statement prominently appears on the principal display panel in accordance with 21 CFR 208.24(d).

3. We recommend unbolding the "Rx only" statement and other statements on the right half of the principal display panel so they do not compete in prominence with critical information on the principal display panel.

4. 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). For the net quantity statement ("1 x 60 mg Single-dose Prefilled Syringe"), we recommend either updating the strength from "60 mg" to "60 mg/mL", or changing the net quantity statement to "1 x Single-dose Prefilled Syringe", to ensure a consistent expression of the strength in accordance with USP General Chapter <7>.

5. We recommend deleting [redacted] (b) (4) as it contributes to visual clutter. Additionally, we recommend revising the storage and handling information on the back panel to read:

> Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light and heat.
> Do not freeze. Avoid excessive shaking.
> Prior to administration, Ospomyv may be allowed to reach room temperature up to 25°C (77°F) in the original container. Once removed

from the refrigerator, Ospomyv may be stored at room temperature for a single period of up to 60 days, but not exceeding the original expiry date. If not used within this period of up to 60 days, Ospomyv may be returned to the refrigerator for 28 days for future use. Do not use Ospomyv after the expiry date printed on the label.

6. We recommend replacing the statement (b) (4) ." with "Recommended Dosage: See Prescribing Information" on the back panel in accordance with 21 CFR 201.55.
7. This product is not intended for patient self-administration, so we recommend removing the text on the side panel that says:

   (b) (4)
   "
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 (b) (4) 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. A placeholder for the 2D data matrix barcode is missing, please add a placeholder for the 2D data matrix barcode to the prefilled syringe carton labeling. We recommend positioning the 2D data matrix barcode near the human-readable portion of the product identifier. See *Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021)*.

APPENDICES: METHODS AND RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 2 presents relevant product information for Ospomyv received on September 10, 2024 from Samsung Bioepis Co., Ltd., and the US-licensed Reference Product (RP).

Table 2. Relevant Product Information for Ospomyv and the US-licensed Reference Product (RP).		
Product Name	Ospomyv	Prolia[b] (BLA 125320)
Initial Approval Date	N/A	June 1, 2010
Nonproprietary Name	denosumab-xxxx	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 a safety guard.	Single-dose prefilled syringe with a safety guard. The prefilled syringe is not made with natural rubber latex.

[b] Prolia [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. Mar 2024. [cited 2024 Sep 24]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/125320s213lbl.pdf

Table 2. Relevant Product Information for Ospomyv and the US-licensed Reference Product (RP).		
Product Name	Ospomyv	Prolia[b] (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, product may be stored at room temperature for a single period of up to 60 days, but not exceeding the original expiry date. If not used within this period of up to 60 days, product may be returned to the refrigerator for 28 days for future use. 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 14 days. Discard if not used within the 14 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,[c] along with postmarket medication error data, we reviewed the following Ospomyv labels and labeling submitted by Samsung Bioepis Co., Ltd.

- Branded Prescribing Information and Medication Guide received on September 10, 2024, available from \\CDSESUB1\evsprod\BLA761392\0024\m1\us\114-labeling\114a-draft-label\draft-labeling-60-mg-tracked.docx
- Unbranded Prescribing Information and Medication Guide received on November 13, 2024, available from \\CDSESUB1\evsprod\BLA761392\0034\m1\us\draft-labeling-unbranded-60-mg-tracked.docx
- Branded and Unbranded Container labels received on February 12, 2024
- Branded and Unbranded Carton labeling received on February 12, 2024
- Branded and Unbranded Professional Sample Container Labels received on February 12, 2024
- Branded and Unbranded Professional Sample Carton Labeling received on February 12, 2024

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

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

APPENDIX C. PREVIOUS DMEPA REVIEWS

On September 24, 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 761392	Ospomyv (denosumab-xxxx) injection	Samsung Bioepis Co., Ltd.	60 mg/mL	Subject of this review	2024-8268

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/s/

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12/13/2024 09:49:43 AM

YEVGENIYA M KOGAN
12/13/2024 05:02:04 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)

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

Date of This Review:	December 13, 2024
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	BLA 761392
Product Name, Dosage Form, and Strength:	Xbryk (denosumab-xxxx)[a] injection, 120 mg/1.7 mL (70 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	Samsung Bioepis Co., Ltd.
FDA Received Date:	February 12, 2024, September 10, 2024, and November 13, 2024
TTT ID #:	2024-8282
DMEPA 1 Safety Evaluator:	Amy J. Bao, PharmD, MPH
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

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

1 INTRODUCTION

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

1.1 BACKGROUND

Xbryk (denosumab-xxxx) 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 761392.

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 unbranded Xbryk Prescribing Information (PI) and determined that it is acceptable from a medication error perspective.

However, the proposed branded Xbryk Prescribing Information (PI), container labels, and carton labeling, and the proposed unbranded Xbryk 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 Samsung Bioepis Co., Ltd. in Section 5.

4 RECOMMENDATIONS FOR THE DIVISION OF GENERAL ENDOCRINOLOGY (DGE)

A. Branded Prescribing Information

1. As currently presented, the proprietary name is denoted by the placeholder "SB16 120 mg vial". We reference our April 26, 2024 Proprietary Name Request Conditionally Acceptable letter informing you that the proprietary name, Xbryk, was found conditionally acceptable. We recommend replacing the placeholder "SB16 120 mg vial" with the conditionally acceptable proprietary name, Xbryk.

5 RECOMMENDATIONS FOR SAMSUNG BIOEPIS CO., LTD.

A. General Comments (Container Labels and Carton Labeling)

1. As currently presented, the proprietary name is denoted by the placeholders "SB16" and "SB16 Vial". We are unable to assess the prominence and readability of the intended presentation of the proprietary name. We reference our April 26, 2024 Proprietary Name Request Conditionally Acceptable letter informing you that the proprietary name, Xbryk, was found conditionally acceptable. We recommend replacing the placeholders "SB16" and "SB16 Vial" with the conditionally acceptable proprietary name, Xbryk, 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. The strength is not clearly differentiated due to the similarity between the (b) (4) color which overlaps with the font color used for the nonproprietary name. Color differentiation is most effective when the color used has no association with a particular feature. We recommend revising the color of the nonproprietary name (consider a black font to align with the dosage form font) or the color of the box surrounding the strength, such that the strength and the nonproprietary name appear in their own unique colors that do not overlap.
3. As currently presented, the format for the expiration date is not defined. We are unable to assess the proposed expiration date format from a medication safety perspective. To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend identifying the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or 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)*.

B. Container Labels

1. As currently presented, the proprietary name and nonproprietary name lack prominence on the principal display panel. We recommend increasing the prominence of the proprietary name and nonproprietary 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. For the branded container labels, move the nonproprietary name so that it appears directly below the proprietary name
3. For the unbranded container labels, we recommend (b) (4) the nonproprietary name "Denosumab-XXXX" already appears as the unbranded name of the product.
4. We recommend increasing the size of the strength color box so that it includes the "(70 mg/mL)" as well.
5. The name of the manufacturer is part of the minimum information that is required to be on small labels and is important for product distinction. We are concerned that the manufacturer information is not readily accessible on the principal display panel. Please move the manufacturer information from the bottom layer of the container label to the front side of the upper layer in accordance with 21 CFR 201.10(i).
6. Please clarify what the orange squares located on the right-hand side of the container labels are intended to represent, and if these will be printed as they appear (a graphic design), or if they are placeholders for something (variable text, a barcode, clear viewing space, etc.).

C. Carton Labeling

1. For the unbranded carton labeling, we note the biological suffix "-XXXX" appears on a separate line from "Denosumab". We recommend keeping the core name and the suffix on the same line of text in order to prevent any misinterpretation of the full nonproprietary name.
2. We note the strength appears on the principal display panel and side panels (b) (4). To decrease cluttering and redundancy, we recommend (b) (4) editing the "120 mg/1.7 mL" that appears in the teal colored area so that it reads "120 mg/1.7 mL (70 mg/mL)".
3. We recommend unbolding the "Rx only" statement so it does not compete in prominence with critical information on the principal display panel.
4. The product strength should be expressed as the quantity per total volume followed by the quantity per milliliter (mL), as described in USP General Chapter <7>, Labeling. We recommend keeping the entirety of the net quantity statement ("1 x 120 mg Single-Dose Vial") on a single line and either updating the strength from "120 mg" to "120 mg/1.7 mL (70 mg/mL)", or changing the net quantity to "1 x Single-Dose Vial", to ensure a consistent expression of the strength in accordance with USP General Chapter <7>.
5. We recommend decreasing the font size and moving the "Single-Dose Vial.", "Discard Unused Portion.", and "Sterile Solution – No Preservative" statements

to the right side of the principal display panel to decrease cluttering of critical information.

6. We recommend deleting [redacted] as it contributes to the visual clutter. Additionally, we recommend revising the storage and handling information on the back panel to read:

   > Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light and heat.
   > Do not freeze. Avoid excessive shaking.
   > Once removed from the refrigerator, Xbryk may be stored at room temperature for a single period of up to 60 days, but not exceeding the original expiry date. If not used within this period of up to 60 days, Xbryk may be returned to the refrigerator for 28 days for future use. Do not use Xbryk after the expiry date printed on the label.

7. We recommend replacing the statement "[redacted]" with "Recommended Dosage: See Prescribing Information" on the back panel in accordance with 21 CFR 201.55.

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 "[redacted]" 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. A placeholder for the 2D data matrix barcode is missing, please add a placeholder for the 2D data matrix barcode to the prefilled syringe carton labeling. We recommend positioning the 2D data matrix barcode near the human-readable portion of the product identifier. See *Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021)*.

APPENDICES: METHODS AND RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 2 presents relevant product information for Xbryk received on September 10, 2024 from Samsung Bioepis Co., Ltd., and the US-licensed Reference Product (RP).

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

Product Name	Xbryk	Xgeva[b] (BLA 125320)
Initial Approval Date	N/A	June 1, 2010
Nonproprietary Name	denosumab-xxxx	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	Single-dose vial (1 vial per carton)	120 mg/1.7 mL in a single-dose vial (1 vial per carton)

[b] Xgeva [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. Jun 2020. [cited 2024 Sep 24]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125320s203lbl.pdf.

Table 2. Relevant Product Information for Xbryk and the US-licensed Reference Product (RP).		
Product Name	Xbryk	Xgeva[b] (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 may be stored at room temperature for a single period of up to 60 days, but not exceeding the original expiry date. If not used within this period of up to 60 days, product may be returned to the refrigerator for 28 days for future use. 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 14 days. Discard if not used within the 14 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	

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,[c] along with postmarket medication error data, we reviewed the following Xbryk labels and labeling submitted by Samsung Bioepis Co., Ltd.

- Branded Prescribing Information received on September 10, 2024, available from \\CDSESUB1\evsprod\BLA761392\0024\m1\us\114-labeling\114a-draft-label\draft-labeling-120-mg-tracked.docx
- Unbranded Prescribing Information received on November 13, 2024, available from \\CDSESUB1\evsprod\BLA761392\0034\m1\us\draft-labeling-unbranded-120-mg-tracked.docx
- Branded and Unbranded Container labels received on February 12, 2024
- Branded and Unbranded Carton labeling received on February 12, 2024
- Branded and Unbranded Professional Sample Container Labels received on February 12, 2024
- Branded and Unbranded Professional Sample Carton Labeling received on February 12, 2024

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

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

APPENDIX C. PREVIOUS DMEPA REVIEWS

On September 24, 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 761392	Xbryk (denosumab-xxxx) injection	Samsung Bioepis Co., Ltd.	120 mg/1.7 mL (70 mg/mL)	Subject of this review	2024-8282

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YEVGENIYA M KOGAN
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OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

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

Date	10/2/2024		
To:	Nowrin Kakon, Regulatory Health Project Manager		
Requesting Center/Office	CDER/OPQ	**Clinical Review Division**	DBRRIV
From	Papatya Kaner OPEQ/OHT3/DHT3C/THT3C3		
Through (Team)	Injection Devices Team OPEQ/OHT3/DHT3C/THT3C1		
Through (Division) *Optional	Shruti Mistry, Assistant Director, Injection Team OPEQ/OHT3/DHT3C/THT3C1		
Subject	ICCR#: 974458 ICC#: 2400162 Submission: BLA 761392 Sponsor: Samsung Bioepis Co., Ltd. Drug/Biologic: Denosumab Indications for Use: Treatment of postmenopausal women with osteoporosis at high risk for fracture		
Recommendation	**Final Recommendation:** ☑ Device Constituent Parts of the Combination Product are Approvable. ☐ Device Constituent Parts of the Combination Product are Approvable with the following Post-Market Requirements/Commitments, ☐ Device Constituent Parts of the Combination Product are Not Approvable with the following CR Deficiencies		
	Comments to Review Team: CDER/OPQ requested CDRH review for this BLA original application because the application has information about a safety pre-filled syringe. A total of four information requests were communicated to Samsung Bioepis on 9/17/2024 and 9/27/2024. They provided acceptable responses to all on 9/23/2024 and 9/30/2024. CDRH does not have any approvability issues.		
	PMC/PMR or CR Deficiencies: N/A		

Digital Signature Concurrence Table		
Reviewer	**Team Lead (TL)**	**Division (*Optional)**
PAPATYA KANER -S Digitally signed by PAPATYA KANER -S Date: 2024.10.02 21:14:06 -04'00'	Shruti N. Mistry -S 2024.10.03 09:14:47 -04'00'	

1. PURPOSE

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

This review will cover the following review areas:

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

CDRH Quality Systems Assessment / Facilities consult not required per internal MAP 5017.7
It was determined that a device quality systems / facilities assessment is not required for this product because the product is not an emergency (i.e., life-saving and essential[2]) treatment that are administered by non-health care professionals.

2. DEVICE DESCRIPTION

The SB16 pre-filled syringe (PFS) is a single use, disposable injection device containing SB16 active substance (denosumab) for subcutaneous injection. SB16 PFS is provided in 60 mg of denosumab in 1.0 mL solution. SB16 Safety PFS comprises of SB16 DP and the device constituent part combined and produced as a single entity. SB16 Safety PFS is intended for use in subcutaneous administration of drug by healthcare professionals (HCPs).

The SB16 Safety PFS is provided fully assembled with the PFS containing a 60 mg of SB16 denosumab for injection and is presented in Figure 1. No further assembly or loading of the drug product is required at the point of use.

Figure 1: Representative Illustration of SB16 Safety PFS

The primary packaging components of SB16 Safety PFS consist of a 1 mL clear glass syringe with staked needle, rigid needle shield, and plunger stopper. The glass syringe, as the primary container closure, contains SB16 DP. The Safety PFS consists of a nude PFS assembled into secondary packaging components including safety shield and plunger rod.

[1] The scope of this review will be limited to the device constituent performance in accordance with ISO 23908:2011 Sharps Injury Protection and FDA guidance Medical Devices with Sharps Injury Prevention Features. Therefore, for a PFS with a needle safety device constituent the review will be limited to needle safety performance requirements and will not cover functions of the primary container (container content, breakloose force, glide force, needle shield removal force, etc.,).
[2] Examples of emergency, life-saving and essential treatments include those used for conditions such as anaphylaxis or cardiac arrest and others in which failure of drug delivery may expose the patient to the reasonable likelihood of serious injury or death.

Requirement	Describe
Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use)	Healthcare professionals use this product to treat postmenopausal women with osteoporosis at high risk for fracture
Injection Site	
Injection tissue and depth of injection	Subcutaneous injection
Needle connection (e.g. luer, slip tip, staked)	Staked
Needle safety type (active or passive)	Passive
Delivered Dose Volume	The SB16 pre-filled syringe (PFS) is provided in 60 mg of denosumab in 1.0 mL solution.
Shelf-life/Storage, including excursions (e.g., 36months, 5C)	36 months when stored at 2-8°C

3. DEVICE PERFORMANCE REVIEW

3.1. Design Verification & Validation

Following tables are obtained from "32r6-medical-device-60mg":

Essential performance requirements of the safety component are highlighted below in Table 3.

Table 3: Essential Performance Requirements for SB16 Safety PFS

Essential Performance Parameters	Acceptance Criteria	Description
Break- loose force	≤ (b) (4) N at (b) (4) mm/min	For injection of the Safety PFS, the break-loose force is represented as the maximum force required to break the static friction of the plunger. The specification for the break- loose force is defined based on the limits of user capabilities and would directly impact the delivery of the medicinal product if the user cannot inject the medicinal product.

Essential Performance Parameters	Acceptance Criteria	Description
Gliding force	≤ (b) (4) N at (b) (4) mm/min	For injection of the Safety PFS, the gliding force is represented as the maximum force required to maintain plunger movement once static friction has been overcome. The specification for the gliding force is defined based on the limits of user capabilities and would directly impact the complete dose if the user cannot inject the medicinal product.
Delivered volume	60 mg PFS: ≥ 1.0 mL	Delivered volume is the volume delivered out of the container after the PFS is pushed with the plunger rod. The delivered volume is established to ensure efficacy during use. Failure to meet dose accuracy requirements is failure to accurately deliver the medicinal product via correct route.
Safety shield activation force	≤ (b) (4) N at (b) (4) mm/min	Safety shield activation force is required to activate the safety shield body after the dosing completion. Failure of the needle safety mechanism might result in unacceptable harm to the patient or user.
Safety shield lockout feature (after injection)	Confirmation of locking after safety shield activation	The safe shield body covers the entire needle by the release of the plunger rod after the injection is completed. The locked safety shield body prevents needle stick injuries. Failure of the needle safety mechanism might result in unacceptable harm to the patient or user.

Sample Size, Acceptance Criteria and Test Results for Design Verification:

- Sample size for SB16 Safety PFS DVT was determined in accordance with Section 9 and Annex F in ISO 11608-1:2022.
- The acceptance criteria of functional performance parameters and the design verification results are summarized in Table 6 to Table 7.

Table 6: Acceptance Criteria of Functional Performance Parameters

Test	Test Item	Acceptance Criteria
Visual inspection	Inspection for damage or defect before the test	Pass
Functional test	Cap removal force[a]	(b) (4) N
	Break-loose force[a]	≤ (b) (4) N
	Gliding force[a]	≤ (b) (4) N
	Safety shield activation force[a]	≤ (b) (4) N
	Delivered volume	≥ 1.0 mL
Confirmation for locking of safety shield activation	Confirmation of locking after safety shield activation	Pass
Leak testing	Inspection for leakage past the plunger stopper seal and the syringe cap	Pass

[a] The functional test was conducted at (b) (4) mm/min.

Table 7: Design Verification Testing Result Summary of SB16 Safety PFS

Pre-conditioning Testing Group	Test Item	Data Type	Sample Size	Result
Operating environment at standard conditions (23 ± 5°C, 50 ± 25%RH)	Visual inspection before test: - Check visible damage and defect	Attribute	120	Pass
	Functional testing: - Cap removal force, break-loose force, gliding force, safety shield activation force, and delivered volume	Variable	30	Pass
	Checking safety shield locking - Confirm locking after safety shield activation	Attribute	120	Pass
Operating environment at cool conditions (5 ± 3°C)	Visual inspection before test: - Check visible damage and defect	Attribute	120	Pass
	Functional testing: - Cap removal force, break-loose force, gliding force, safety shield activation force, and delivered volume	Variable	30	Pass
	Checking safety shield locking - Confirm locking after safety shield activation	Attribute	120	Pass
Operating environment at warm conditions (40 ± 2°C, 50 ± 10%RH)	Visual inspection before test: - Check visible damage and defect	Attribute	120	Pass
	Functional testing: - Cap removal force, break-loose force, gliding force, safety shield activation force, and delivered volume	Variable	30	Pass
	Checking safety shield locking - Confirm locking after safety shield activation	Attribute	120	Pass
Leak testing	Leak testing - Confirm the leakage from either cap or plunger rod	Variable	60	Pass

Sharps Injury Prevention:

Sharp prevention study was conducted by safety shield supplier to confirm sharp prevention feature of safety shield. SB16 Safety PFS is an integrated injection system of pre-filled ISO standard glass 1 mL syringes and safety shield which is a non-sterile and disposable safety device with a passive activation of the needle covering system. SB16 Safety PFS has been developed to be used by healthcare workers for subcutaneous (SC) manual injections.

50 participants were selected to test 10 devices each, for a total of 500 Safety PFS filled with saline solution. The 50 user participants consisted of 20 health care professionals (HCPs), notably nurses, (b) (4) Participants were chosen as representative of the population of intended users; demographics met the inclusion criteria as per the protocol (Table 20).

Table 20: Chosen Participants as Representative of the Population of Intended Users

User Group	Inclusion Criteria (underline) and Demographics	Number of Participants
HCP	- HCP from different facilities: 100% hospital, 5% private practice, 5% medical clinic, 5% other. - HCP from different practice types: 55% registered nurses, 5% clinical specialist, 5% oncology specialist, 5% hepatology specialist, 15% other. - Performing a minimum of 20 injections per month: 80% gave more than 20 injections per month. - Experience in medication injection for rheumatoid arthritis, multiple sclerosis, Crohn's disease, cancer and psoriasis.	20

User Group	Inclusion Criteria (underline) and Demographics	Number of Participants
	- Right/left handedness representative of human population: 90% were right handed. - 90% of nurses had small or extra-small hands. - 45% had prior experience of needlestick injury.	
	(b) (4)	

Reviewer Comments:

- For the safety device's design verification, Sponsor's tested sample sizes are included in Tables 6-7 above, which are in compliance with the recommended minimum sample sizes in Table 3, ISO 11608-1:2022.
- Please see the Information Request #1 (resolved) below for our question regarding the safety device's simulated use testing per ISO 23908: 2011.

Information Request #1	(b) (4)
Sponsor Response	

	(b) (4)
Reviewer Comments	Sponsor provided design verification testing for the needle safety device under intended use conditions including shipping and drop through simulated transportation study and hence, it was not subject to any pre-conditioning prior to the simulated clinical use testing. 50 participants were selected to test 10 devices each, for a total of 500 Safety PFS filled with saline solution. Sponsor's pre-conditioning approach is reasonable and sample size is appropriate; hence the response is acceptable.
Response Adequate:	☑ **Yes** ☐ **No, See IR #**

Biocompatibility:

In accordance with ISO 10993-1, each component of SB16 Safety PFS was categorized based on the nature and duration of body contact, and the biological endpoints were assessed as following Table 8.

Table 8: Biological Endpoints of SB16 Safety PFS

Component		Medical Device Categorization by		Endpoint of Biological Evaluation						
		Nature of Body Contact	Contact Duration[a]	Physical and/or Chemical Information	Cytotoxicity	Sensitization	Irritation or Intracutaneous Reactivity	Material Mediated Pyrogenicity	Acute Systemic Toxicity	Hemocompatibility
SB16 Safety PFS	Syringe (with needle)	Surface medical device - Intact skin and Externally communicating medical device - Blood path	A (limited exposure)	X[b]	E[c]	E	E	E	E	E
	Plunger stopper	Externally communicating medical device - (indirect) Blood path		X	E	E	E	E	E	E
	Plunger rod	Surface medical device - Intact skin		X	E	E	E	N/A[d]	N/A	N/A
	Safety shield	Surface medical device - Intact skin		X	E	E	E	N/A	N/A	N/A

[a] Contact duration: A-limited (≤ 24 hours), B-prolonged (> 24 hours to 30 days), C-long term (> 30 days)
[b] X means prerequisite information needed for a risk assessment.
[c] E means endpoints to be evaluated in the risk assessment (either through the use of existing data, additional endpoint-specific testing, or a rationale for why assessment of the endpoint does not require an additional data set).
[d] Not applicable

The biological evaluation of each device components for SB16 Safety PFS product was performed by the supplier, (b) (4) according to ISO 10993 series. The results of biological evaluation are summarized in Table 9.

Table 9: Summary of Biological Evaluation Results of SB16 Safety PFS

Component		Results of Biological Evaluation					
		Cytotoxicity	Sensitization	Irritation or Intracutaneous Reactivity	Material Mediated Pyrogenicity	Acute Systemic Toxicity	Hemocompatibility
SB16 Safety PFS	Syringe (with needle)	Pass	Pass	Pass	Pass	Pass	Pass
	Plunger Stopper	Pass	Pass	Pass	Pass	Pass	Pass
	Plunger Rod	Pass	Pass	Pass	N/A	N/A	N/A
	Safety Shield	Pass	Pass	Pass	N/A	N/A	N/A

Based on the results of the biological evaluation of each component, it is considered that SB16 Safety PFS is biocompatible and safe for the end user.

3.2. Validation

Stability Summary and Conclusion:

SB16 60 mg Safety PFS batches were placed on long term condition at 5 ± 3°C and accelerated condition at 25 ± 2°C/60 ± 5%RH. The accelerated aging study condition is intended to provide sufficient evidence for shelf life claim of the Safety PFS until data from long term studies are available in accordance with ASTM F1980.

The stability program for SB16 Safety PFS is summarized in Table 11. The details on each study type are provided in this section.

Table 11: Stability Program of SB16 Safety PFS

Study Type	Presentation	Batch No.	Storage Conditions	Data Available (Month)[a]
Long-term condition	60 mg PFS	F23160V1 F23160V2 F23160V3	5 ± 3°C,	0, 1, 3, 6, 12, 24[b], 36[b], 48[b]
Accelerated aging condition	60 mg PFS	F23160V1 F23160V2 F23160V3	25 ± 2°C, 60 ± 5% RH	**0, 1 (RTE 4 months),** 3 (RTE 1 year), 6 (RTE 2 years), 9 (RTE 3 years), 12 (RTE 4 years)

RTE: real time equivalent

[a] Completed time points are in bold.

[b] At 24, 36, and 48 months time points, the Safety PFS is stored at room temperature (RT) for additional (b) (4) to support the in-use storage condition and duration for patient convenience.

Accelerated Aging:

For the accelerated aging study, the method for calculating accelerated aging time (AAT) equivalent to the real time aging period and the accelerated aging factor (AAF) is calculated based on ASTM F1980. The following formula is used to calculate the storage periods:

- Accelerated Aging Factor (AAF) = $Q10[(TAA-TAT)]/10$

$Q_{10} = 2$; an aging factor for 10°C increase or decrease in temperature

T_{AA}: Chamber temperature of accelerated aging (°C)

T_{AT}: Ambient temperature

- Accelerated Aging Time (AAT) = Desired real time/AAF

The time points for analysis for the accelerated aging studies are determined based on the calculated AAT.

Stability Protocol:

Table 12: Stability Testing Schedule for Long Term Study

Test	Acceptance Criteria	Test Interval (Month)							
		0	1	3	6	12	24[a]	36[a]	48[a]
Visual inspection	Pass	X	X	X	X	X	X	X	X
Cap removal force	(b) (4) N at (b) (4) mm/min	X	X	X	X	X	X	X	X
Break-loose force	≤ (b) (4) N at (b) (4) mm/min	X	X	X	X	X	X	X	X
Gliding force	≤ (b) (4) N at (b) (4) mm/min	X	X	X	X	X	X	X	X
Safety-shield activation force	≤ (b) (4) N at (b) (4) mm/min	X	X	X	X	X	X	X	X
Delivered volume	≥ 1.0 mL	X	X	X	X	X	X	X	X
Confirm the lock after safety-shield activation	Pass	X	X	X	X	X	X	X	X
Container closure integrity test (CCIT)	Pass	X	N/A	N/A	N/A	X	X	X	X

[a] At 24, 36, and 48 month time points, the PFS is stored at room temperature (RT) for additional (b) (4) to support the in-use storage condition and duration for patient convenience.

Table 13: Stability Testing Schedule for Accelerated Aging Study

Test	Acceptance Criteria	Test Interval (Month)					
		0[a]	1 (RTE 4 months)	3 (RTE 1 year)	6 (RTE 2 years)	9 (RTE 3 years)	12 (RTE 4 years)
Visual inspection	Pass	X	X	X	X	X	X
Cap removal force	(b) (4) N at (b) (4) m/min	X	X	X	X	X	X
Break-loose force	≤ (b) (4) N at (b) (4) m/min	X	X	X	X	X	X
Gliding force	≤ (b) (4) N at (b) (4) m/min	X	X	X	X	X	X
Safety-shield activation force	≤ (b) (4) N at (b) (4) m/min	X	X	X	X	X	X
Delivered volume	≥ 1.0 mL	X	X	X	X	X	X
Confirm the lock after safety-shield activation	Pass	X	X	X	X	X	X

Test	Acceptance Criteria	Test Interval (Month)					
		0[a]	1 (RTE 4 months)	3 (RTE 1 year)	6 (RTE 2 years)	9 (RTE 3 years)	12 (RTE 4 years)
Container closure integrity test (CCIT)	Pass	X	N/A	X	N/A	X	X

[a] Initial time point results for real time aging study were used for the initial time point.

Proposed Shelf-life and Storage Condition:
The proposed shelf-life for SB16 Safety PFS is 36 months when stored at 2-8°C. Sponsor stated that this shelf-life is based on the 9-month stability data of accelerated aging study that will become available during the review process. Currently, the stability data have conformed to the acceptance criteria at the accelerated aging condition for up to (b) (4) which is equivalent to (b) (4) of real-time aging.

Reviewer Comments:
- Please see the Information Request #2 (resolved) below for our question regarding the safety device's stability program and Sponsor's response.

Information Request #2	(b) (4)
Sponsor Response	
Reviewer Comments	Samsung Bioepis provided the 9-month stability data of accelerated aging study, and we updated "Stability Summary and Conclusion" section above to include the updated results. The response is acceptable.
Response Adequate:	☑ **Yes** ☐ **No, See IR #**

Simulated Shipping Study Summary obtained from Module 3.2.P.3.5 Process Validation and/or Evaluation under Sequence 0025 (dated 9/11/2024):

Sample Conditioning:
Samples were stored at 5 ± 3°C. Samples underwent stabilisation at room temperature (RT, 23 ± 5°C / 50 ± 25% RH) for at least 4 hours after chamber-out before testing.

Test Methods:
Testing was performed in accordance with test protocol (b) (4) P3998 V1 and the referenced documents. All test methods in this study were validated; this can be seen in SB16 method validation test protocol (b) (4) P2866-B Rev1 and SB16 method validation test report (b) (4) 2866/3989.

Test Results:

Test Sequence		Acceptance Criteria	Acceptance Criteria Met for All Samples?
1	Pre-Test Visual Inspection	All samples must not have any significant defects, such as: • Cracks in the body and/or component of the PFS that might impact safe functioning. • Compromised assembly bonds, joints and alignments that might impact safe functioning. • Cracked containers or obvious loss of contents.	Yes
2A	Cap Removal Force	The force to remove the cap must be greater than or equal to (b) (4) N and less than or equal to (b) (4) N (at (b) (4) mm/min), for all samples.	Yes
2B	Break Loose Force	The maximum break loose force must be less than or equal to (b) (4) N (at (b) (4) mm/min), for all samples.	Yes
	Gliding Force	The maximum gliding force must be less than or equal to (b) (4) N (at (b) (4) mm/min), for all samples.	Yes
2C	Safety Shield Activation Force	The safety shield activation force must be less than or equal to (b) (4) N (at (b) (4) mm/min), for all samples.	Yes
2D	Dose Accuracy (Full Injection)	The dose accuracy result must be greater than or equal to 1.0 mL (Lower Specification Limit (V_{LSL})), for all samples.	Yes
3	Post-Test Attribute Test	Ensure that the safety shield is well-locked after the injection is complete, for all samples.	Yes

Reviewer Comments:
- Please see the Information Request #3 (resolved) below for our question regarding the safety device's simulated shipping study and Sponsor's response.

Information Request #3	(b) (4)
Sponsor Response	

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	(b) (4)
Reviewer Comments	Samsung Bioepis provided a summary of the physical stress conditions applied during the simulated transportation study and the functional test methods performed after the physical stress. For additional details, they referenced the relevant sections of their shipping qualification report provided on 9/11/2024 in Module 3.2.P.3.5 Process Validation and/or Evaluation. Their methods are in compliance with ASTM D4169-16; and hence, the response is acceptable.
Response Adequate:	☑ **Yes** ☐ **No, See IR #**

4. CONTROL STRATEGY REVIEW

Description of Manufacturing Process and Process Controls of SB16 Safety PFS:
The (b) (4) is carried out at (b) (4) schematic diagram of the manufacturing process for SB16 Safety PFS is provided in Figure 5.

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Release Specifications of SB16 Safety PFS:

(b) (4) release testing of SB16 Safety PFS is conducted, as presented in Table 29. The measurement of functional testing is to ensure that the SB16 Safety PFS functions properly and prevents needle stick injuries.

Table 29: Functional Release Testing Results of SB16 Safety PFS Assembly PV Batches

Test	Acceptable Range	Result		
		F23160V1	F23160V2	F23160V3
Break-loose force	≤ (b) (4) at (b) (4) mm/min	32 of 32 Pass	32 of 32 Pass	32 of 32 Pass
Gliding force	≤ (b) (4) at (b) (4) mm/min	32 of 32 Pass	32 of 32 Pass	32 of 32 Pass
Safety shield activating force	≤ (b) (4) at (b) (4) mm/min	32 of 32 Pass	32 of 32 Pass	32 of 32 Pass
Confirmation of the locking after safety shield activation	Pass	32 of 32 Pass	32 of 32 Pass	32 of 32 Pass

Reviewer Comments

- Please see the Information Request #4 (resolved) below for our question regarding the safety device's design control strategy and Sponsor's response.

Information Request #4	(b) (4)
Sponsor Response	
Reviewer Comments	Samsung Bioepis clarified (b) (4) . The details of their release specifications for lot release controls are provided in the tables above. Sponsor's control strategy is acceptable.
Response Adequate:	☑ **Yes** ☐ **No, See IR #**

<<END OF REVIEW>>

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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:	July 08, 2024
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	BLA 761392
Product Type:	Combination Product (Biologic-Device)
Product Name, Dosage Form and Strength:	SB16[a] (denosumab-xxxx)[b] injection, 60 mg/mL
Device Constituent:	Prefilled Syringe with Needle Safety Guard
Rx or OTC:	Rx
Applicant/Sponsor Name:	Samsung Bioepis Co., Ltd (Samsung)
Submission Date:	February 12, 2024
OSE TTT #:	2024-8270
DMEPA 1 Safety Evaluator:	Avinash Konkani, PhD, MS, BE
DMEPA 1 Team Leader (Acting):	Matthew Barlow, RN, BSN
DMEPA 1 Associate Director for Human Factors:	Ariane O. Conrad, PharmD, BCACP, CDCES, FISMP

[a] SB16 has been developed as a proposed interchangeable biosimilar to US-licensed Prolia. The proprietary name, Xbryk was found conditionally acceptable by DMEPA on April 15, 2024. For the purposes of this review, "SB16" is used throughout the review to refer to this product.

[b] The nonproprietary name suffix for this BLA has not yet been determined. Therefore, the placeholder "denosumab-xxxx" is used to refer to the non-proprietary name for this product and is not intended to be included in the final labels and labeling.

1 REASON FOR REVIEW

On February 12, 2024, Samsung submitted Biologics License Application (BLA) 761392 that included a use-related risk analysis (URRA) and comparative analyses (CA) to support their marketing application for SB16 (denosumab-xxxx) injection, 60 mg/mL as a proposed interchangeable biosimilar to US-Licensed Prolia (hereafter, called Prolia).

2 BACKGROUND

SB16 is a single ingredient combination product with a single-dose prefilled syringe (PFS) with a needle safety guard device constituent part, intended for administration by healthcare professionals. SB16 is a RANK 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 August 02, 2021, Samsung submitted a URRA and CA, under IND 141802 to support their future marketing application for SB16 PFS as a proposed biosimilar to Prolia PFS. On December 02, 2021, we reviewed the URRA and CA and determined Samsung does not need to submit HF validation study results to support their future marketing application for SB16 PFS. We also advised Samsung that additional human factors considerations may apply if they modified the product user interface.[c]

On July 14, 2023, Samsung submitted a Biosimilar Product Development (BPD) Type 4 meeting request under IND 141802 to discuss the planned marketing application for SB16 as an interchangeable biosimilar to Prolia. The teleconference meeting with Samsung was held on September 22, 2023. In the Agency's final meeting minutes dated October 20, 2023, we requested Samsung "*confirm that there have been no changes to your user interface that would necessitate changes to your URRA and CA in the context of interchangeability since the August 2, 2021, prior submission."* with their BLA submission[d].

On February 12, 2024, Samsung submitted their marketing application under BLA 761392 for SB16 PFS as a proposed interchangeable biosimilar to Prolia. The submission included changes to their URRA, CA, and product user interface (in tabular format) as agreed upon based on the Agency's final meeting minutes dated October 20, 2023, under IND 141802[d]. However, we

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[c] Lee, S. Use-Related Risk Analysis and Comparative Analyses review for SB16 Injection, 60 mg/mL (IND 141802). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 DEC 02. TTT No.: 2021-1648. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8062e58b

[d] Johnson, J. Meeting minutes for SB16 Injection (IND 141802). Silver Spring (MD): FDA, CDER, OND, DGE (US); 2023 OCT 20. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80700bcf

noted that Section (b) (4) Preparation and Administration of Samsung's proposed Prescribing Information (PI) included preparation and administration instructions for healthcare professionals for the PFS, which were not consistent with the corresponding text in Section 2.4 Preparation and Administration of the Prolia PI.

As such, we issued an information request (IR) to Samsung on April 03, 2024, recommending Samsung that the preparation and administration instructions for the PFS in (b) (4) the proposed PI are revised for consistency with the corresponding text in Section 2.4 Preparation and Administration of the Prolia PI, except for information that is specific to their proposed product and necessary to inform safe and effective use. Therefore, we requested Samsung to submit an updated PI and CA.

Subsequently, on April 05, 2024, Samsung provided the following in response to the IR:

- Updated PI, which included an updated section (b) (4) (Preparation and Administration) of the proposed PI that is consistent with corresponding text in the US-licensed Prolia PI Section 2.4.
- Updated CA

In addition, Samsung indicated in the updated CA[e] that they made the following changes to the SB16 PFS, product user interface (PI and labeling), since their submission on August 02, 2021 under IND 141802.

- Changes to PI:
  - Dosage form and strength have been added when indicating the product.
  - Section (b) (4) Expression of drug color has been changed (b) (4) to slightly yellow.
  - Section (b) (4) The sentence "DO NOT put needle cap back on needle" has been relocated (b) (4) to Step 2 to be consistent with the Prolia PI.
  - Section (b) (4) The sentence " (b) (4) " has been removed to be consistent with the Prolia PI.
  - Section (b) (4): The sentence "DO NOT put the needle cap back on the used syringe" has been added to be consistent with the Prolia PI.
  - Storage information has been changed, based on product quality data, as below:
    - Allowable period for room temperature storage changed (b) (4) to 60 days.
    - Instructions related to re-refrigeration has been added.

- Changes to Carton structure and artwork design:
  - Open tab has been incorporated to facilitate the opening of the carton.
  - Brand color has been changed (b) (4) to orange.

[e] Updated CA includes the changes to the SB16 product user interface (page 60 to 67). Updated CA can be accessible in EDR via: \\CDSESUB1\EVSPROD\bla761392\0005\m5\53-clin-stud-rep\535-rep-effic-safety-stud\osteoporosis\5354-other-stud-rep\urra\urra.pdf.

- Changes to labeling: Updated corporate design color, product manufacturer information, drug formulation, storage information, logo, and formatting.

Based on our independent expert review, we determined that these 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 study.

3 CONCLUSION

Based on the aforementioned information, we determined that Samsung does not need to submit comparative use human factors study results with their marketing application for SB16 (denosumab-xxxx) injection, 60 mg/mL, PFS, as a proposed interchangeable biosimilar to Prolia. We have no HF recommendations for this marketing application.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. USE RELATED RISK ANAYLYSIS, COMPARATIVE ANALYSES AND HF-RELATED SUPPORTING DOCUMENTS

- Use-Related Risk Analysis, Comparative Analyses (page 14 to 56) and changes of SB16 and Prolia PFS User Interface (page 59 to 66) submission dated February 12, 2024, can be accessible in EDR via: \\CDSESUB1\EVSPROD\bla761392\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\osteoporosis\5354-other-stud-rep\urra\urra.pdf

- Product information (i.e., Full Prescribing Information and Instructions for Use) submission dated February 12, 2024, can be accessible in EDR via: \\CDSESUB1\EVSPROD\bla761392\0001\m1\us\114-labeling\114a-draft-label\draft-labeling-60-mg-clean.docx

APPENDIX B. INFORMATION REQUESTS ISSUED DURING THE REVIEW

April 03, 2024, we issued an information request (IR) recommending Samsung that section (b) (4) (Preparation and Administration) of their proposed Prescribing Information's (PI) instructions for healthcare professionals on preparation and administration of the prefilled syringe, should be consistent with the corresponding text in the US-licensed Prolia PI Section 2.4 (Preparation and Administration), except for information that is specific to their proposed product and necessary to inform safe and effective use. Samsung provided an acceptable response on April 05, 2024, as listed below:

- Use-Related Risk Analysis, updated Comparative Analyses (page 13 to 56) and changes of SB16 and Prolia PFS User Interface (page 60 to 67), can be accessible in EDR via: \\CDSESUB1\EVSPROD\bla761392\0005\m5\53-clin-stud-rep\535-rep-effic-safety-stud\osteoporosis\5354-other-stud-rep\urra\urra.pdf

- Updated Product information (i.e., Full Prescribing Information and Instructions for Use) can be accessible in EDR via: \\CDSESUB1\EVSPROD\bla761392\0005\m1\us\114-labeling\114a-draft-label\draft-labeling-60-mg-clean.docx

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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: 5/9/2024

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 on-site inspections**

RE: BLA 761392

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

Rationale

PPD Development, Austin: The Office of Regulatory Affairs (ORA) conducted an inspection for the clinical site in January 2022. The inspection was conducted under the following submissions: NDAs non-responsive .

OSIS concluded that data from the reviewed studies were reliable.

(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 non-responsive .

OSIS concluded that data from the reviewed studies were reliable.

Sites

Facility Type	Facility Name	Facility Address
Clinical	PPD Development, L.P.	7551 Metro Center Drive, Suite 200, Austin, TX
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/

WENDY NG
05/09/2024 02:39:13 PM