

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761404Orig2s000

OTHER REVIEW(S)

Memorandum to File

Date	February 27, 2025
Application Type	BLA
Application Number(s)	761404
Proper Name	denosumab-bmwo
Trade Name	Osenvelt
Product Code	CT-P41
Applicant	Celltrion, Inc.

Celltrion, Inc. submitted a 351(k) BLA seeking licensure of CT-P41 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 Celltrion's proposed interchangeable biosimilar to Xgeva. Therefore, the approved labeling for that product (with a conditionally approved proprietary name “Osenvelt”) 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
02/27/2025 05:32:38 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 24, 2025
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	BLA 761404
Product Name, Dosage Form, and Strength:	Stoboclo (denosumab- bmwo) injection, 60 mg/mL
Applicant Name:	Celltrion, Inc. (Celltrion)
FDA Received Date:	February 18, 2025
TTT ID #:	2023-7341-4
DMEPA 1 Safety Evaluator:	Peggy Rahbani, PharmD, BCPS
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 PURPOSE OF MEMORANDUM

Celltrion, Inc. submitted revised carton labeling received on February 18, 2025, for Stoboclo. The Division of General Endocrinology (DGE) requested that we review the revised carton labeling for Stoboclo (Appendix A) to determine if it is acceptable from a medication error perspective. The revision is in response to Information Request (IR) that was sent by DGE to the Applicant on February 13, 2025, with the following comments:

- Stoboclo carton labeling: For consistency with Section 2.3 of the Prescribing Information, we recommend revising the statement “(b) (4)” to “Stoboclo should be administered by a healthcare provider”.

2 CONCLUSION

Celltrion, Inc. implemented all of our recommendations and we have no additional recommendations at this time.

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/s/

PEGGY M RAHBANI
02/24/2025 09:46:46 AM

YEVGENIYA M KOGAN
02/24/2025 12:53:30 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 24, 2025
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	BLA 761404
Product Name, Dosage Form, and Strength:	Osenvelt (denosumab- bmwo) injection, 120 mg/1.7 mL (70 mg/mL)
Applicant Name:	Celltrion, Inc. (Celltrion)
FDA Received Date:	February 18, 2025
TTT ID #:	2023-7435-4
DMEPA 1 Safety Evaluator:	Peggy Rahbani, PharmD, BCPS
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 PURPOSE OF MEMORANDUM

Celltrion, Inc. submitted revised carton labeling received on February 18, 2025, for Osenvelt. The Division of General Endocrinology (DGE) requested that we review the revised carton labeling for Osenvelt (Appendix A) to determine if it is acceptable from a medication error perspective. The revision is in response to Information Request (IR) that was sent by DGE to the Applicant on February 13, 2025, with the following comments:

- Osenvelt carton labeling: For consistency with our concurrent recommendations to add the statement “Osenvelt should be administered by a healthcare provider” to Section 2.1 of the Prescribing Information, we recommend adding the statement, “Osenvelt should be administered by a healthcare provider”, to the principal display panel of the Osenvelt carton labeling.

2 CONCLUSION

Celltrion, Inc. implemented all of our recommendations and we have no additional recommendations at this time.

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

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/s/

PEGGY M RAHBANI
02/24/2025 09:47:38 AM

YEVGENIYA M KOGAN
02/24/2025 12:55:29 PM

MEMORANDUM

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

DATE: November 5, 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: Amended Review of Clinical Inspection at Cha Bundang
Medical Center, Seongnam, Republic of Korea

1. Inspection Summary

The amendment is to update OSIS review finalized on 11/03/2024 to update OSIS evaluation of discussion item #1 and the recommendation to review division.

The Office of Study Integrity and Surveillance (OSIS) arranged a clinical inspection of study CT-P41 1.2 (BLA 761404, Denosumab injection) conducted at Cha Bundang Medical Center, Seongnam, Republic of Korea.

Form FDA 483 was not issued to Cha Bundang Medical Center, Seongnam, Republic of Korea. There were five discussion items detailed in the following sections. Based on the inspection finding and my review, I recommend the review division to evaluate the impact of 10 days gap instead of protocol required 2 weeks gap between COVID-19 vaccination and IP administration of subject (b) (6) on the data for the audit study CT-P41 1.2.

2. Inspected Study

BLA 761404

Study Number: CT-P41 1.2

Study Title: "A Randomized, Double-blind, Two-arm, Parallel group, Single-dose, Phase I Study to Compare the Pharmacokinetics, Pharmacodynamics and Safety between CT-P41 and US-licensed Prolia in Healthy Male Subjects"

Dates of study conduct: October 06, 2021 - October 20, 2022

Clinical site: CHA Bundang Medical Center
64 Yatap-Ro, Bundang-Gu
Seongnam, 13520, Republic of Korea

Principal Investigator: Anhye Kim, M.D., Ph.D.

3. Inspectional Findings

3.1 Cha Bundang Medical Center, Seongnam, Republic of Korea

ORA investigator Tyanna N. Hadley inspected Cha Bundang Medical Center, Seongnam, Republic of Korea from August 12 - 16, 2024.

3.1.1 Previous Inspection

OSIS has no inspection history.

3.1.2 Current Inspection

The current inspection included auditing the following items:

- Case report forms (CRFs)
- Informed consent process
- Protocol deviations
- Institutional Review Board approvals
- Randomization
- Test article accountability, and storage
- Adverse events

3.1.3 Inspection findings

At the conclusion of the inspection, investigator Tyanna N Hadley did not issue Form FDA 483. Five discussion items were communicated with management as the following:

Discussion item 1: Eligibility criteria included in subject screening questionnaires

ORA investigator observed subject (b) (6) appeared to meet eligibility criteria at screening and was enrolled in the study. However, following IP administration, the site became aware the subject had received a COVID-19 vaccine within two weeks prior

to IP administration meeting exclusion criterion #5
(Attachment 1: Ex15).

OSIS Evaluation 1:

According to the study protocol, exclusion criteria #5 include that COVID-19 vaccines are prohibited for 2 weeks prior or after the study drug administration. IP administration date for Subject (b) (6) was (b) (6). However, on (b) (6) the subject stated that he received a COVID-19 vaccine on (b) (6). It appears there is only 10 days gap between the subject's receiving COVID-19 vaccine and the subject receiving IP. However, there was no record to support his statement of receipt of a COVID-19 vaccine. Therefore, there is lack of evidence that this discussion item #1 is a protocol violation. Thus, I recommend the review division to evaluate the impact of 10 days gap instead of protocol required 2 weeks gap between COVID-19 vaccination and IP administration of subject (b) (6) on the data for the audit study CT-P41 1.2.

Discussion item 2: Incomplete documentation of subject withdrawal

Subject (b) (6) withdrew from study protocol CT-P41 1.2 prior to completion. Source records did not completely document the circumstances surrounding the subject's withdrawal on (b) (6). According to the end of study worksheet, the reason for subject withdrawal was "withdrawal by subject" (Attachment 2: Ex24, page 1 of 5). The subject's early withdrawal visit worksheet did not document additional comments (Attachment 2: Ex24, page 3 of 5).

OSIS Evaluation 2:

According to the protocol, subjects have the right to withdraw from the study at any time for any reason. The form "worksheet_end of study" appropriately captures the reason for withdrawal (Attachment 2: Ex24, page 1 of 5) and additional comments on the subject's early withdrawal visit worksheet are optional. In addition, this subject is reported as discontinued in Listing 16.2.1. Thus, the discussion item has no impact on reliability of the data or human subject protection for the inspected study CT-P41 1.2.

Discussion item 3: Ensuring evaluation of repetitive abnormal laboratory abnormalities for potential adverse events

ORA investigator observed there were elevated laboratory results which were not reported as adverse events. Subject (b) (6) had several elevated creatinine kinase (CK) laboratory results which were documented as not clinically significant and, therefore, not assessed as adverse events (Attachment 3: Ex25).

Additionally, the subject's triglyceride and cholesterol values became elevated during the study which were not considered by the investigator to be adverse events. ORA investigator observed the firm reviewed and followed-up with the subject's laboratory results, however, the source documentation did not completely describe the investigator's evaluation of the abnormalities for potential adverse events.

OSIS Evaluation 3:

According to the EIR, ORA investigator confirmed that the firm reviewed and followed-up with the subject's laboratory results, but found that the source documentation did not completely describe the investigator's evaluation of the abnormalities for potential adverse events. The EIR did not provide specific examples of the source documents lacking documentation of the investigator's evaluation. Furthermore, despite the discussion item, EIR states that it was verified that the CI reviewed all the elevated laboratory results and followed up with subjects accordingly. Therefore, taken all the information together, I conclude that the discussion item does not impact reliability of the data or human subject protection for the inspected study CT-P41 1.2.

Discussion item 4: Retrospective modification of a study visit worksheet

ORA investigator observed subject (b) (6)'s screening worksheet was retrospectively modified to document the presence of varicose veins. The subject was screened on (b) (6). However, the screening worksheet noted a medical history of varicose veins was reported on (b) (6) (**Attachment 4: Ex26, page 5 of 10**). The note identifies the subject had not reported varicose veins in their medical history until (b) (6), although the screening worksheet otherwise appears the medical history may have been entered at the time of screening (**Attachment 4: Ex26, page 3 of 10**).

OSIS Evaluation 4:

There was a script on page 5, stating (in Korean) that the subject reported lower extremity varicose vein based on his memory on (b) (6) with possible clinical investigator's signature (**Attachment 4: Ex26, page 5 of 10**). Therefore, the written note "Varicose Vein of Lower Extremities, 2017, uK" (Year (b) (6), Month Unknown) on the (b) (6) screening worksheet (**Attachment 4: Ex26, page 3 of 10**), was not entered at screening (b) (6), and most likely entered on (b) (6) based on the contents of the two written notes. Thus, the discussion item does not impact reliability of the data or human subject protection for the inspected study CT-P41 1.2.

Discussion item 5: Time was incorrect on main sample storage refrigerator

During the facility walkthrough, ORA investigator observed embedded refrigerator time display was approximately eight minutes ahead of the actual time. The refrigerator had been calibrated 07Feb2024. Yet, the embedded refrigerator time display was inaccurate.

OSIS Evaluation 5:

The embedded refrigerator time display should be accurate to show the actual time. (b) (6) Clinical Research Coordinator (CRC) for the study, informed ORA investigator a continuous temperature monitor is used to record the time of temperature recordings, not the embedded refrigerator time display. Therefore, the discussion item does not impact reliability of the data for the inspected study CT-P41 1.2.

Attachment 1: Ex15_Subject	(b) (6)	PD Email and Translation
Attachment 2: Ex24_Subject		Withdrawal Worksheets
Attachment 3: Ex25_Subject		Laboratory Results
Attachment 4: Ex26_Subject		Worksheets and Translation

Draft: XC 10/17/2024, 10/24/2024, 10/25/2024, 10/29/2024,
10/30/2024, 10/31/2024, 11/1/2024, 11/5/2024
Edit: MO 10/18/2024, 10/29/2024, 11/5/2024; JC 10/24/2024,
10/29/2024, 10/30/2024, 10/31/2024, 11/1/2024

OSIS File: BE 10125

eNSpect assignment ID: 240996
eNSpect operation ID: 280872

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/s/

XIKUI CHEN
11/05/2024 02:08:13 PM

MEI OU
11/05/2024 02:09:28 PM

SEONGEUN CHO
11/05/2024 02:12:24 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: October 30, 2024

To: Noreen Cabellon, MS
Regulatory Project Manager
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 Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (nonproprietary name): [CT-P41] Stoboclo (denosumab-bmwo)¹

Dosage Form and Route: injection, for subcutaneous use

Application Type/Number: BLA 761404

Applicant: PAREXEL International on behalf of CELLTRION, Inc.

¹ CT-P41 has been developed as a proposed interchangeable biosimilar with US-licensed Prolia (denosumab). The proposed proprietary name, Stoboclo, was found conditionally acceptable on February 28, 2024. The nonproprietary name, denosumab-bmwo, was found conditionally acceptable on August 12, 2024.

1 INTRODUCTION

On November 30, 2023, PAREXEL International on behalf of CELLTRION, Inc., submitted for the Agency's review a Biologics License Application (BLA) 761404 [CT-P41] Stoboclo (denosumab-bmwo) injection, for subcutaneous use. As described by the Applicant, this BLA is "a proposed interchangeable biosimilar product to US-licensed Prolia® (denosumab)" that is "seeking approval for all indications that are currently approved for US-Prolia, which is as follows:

- 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"

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 January 26, 2024, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for [CT-P41] Stoboclo (denosumab-bmwo) injection, for subcutaneous use.

2 MATERIAL REVIEWED

- Draft [CT-P41] Stoboclo (denosumab-bmwo) MG received on November 30, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 4, 2024.
- Draft [CT-P41] Stoboclo (denosumab-bmwo) Prescribing Information (PI) received on November 30, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 4, 2024.
- Approved Prolia (denosumab) 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 the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (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
- ensured that the MG meets 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/

LONICE J CARTER
10/30/2024 01:36:18 PM

MEENA R SAVANI
10/30/2024 01:43:31 PM

MARCIA B WILLIAMS
10/30/2024 02:26:45 PM

LASHAWN M GRIFFITHS
10/30/2024 02:35:24 PM

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

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

Memorandum

Date: October 11, 2024

To: Noreen Cabellon, Regulatory Project Manager
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 Stoboclo® (denosumab-xxxx) injection, for subcutaneous use

BLA: 761404

Background:

In response to DGE's consult request dated January 26, 2024, OPDP has reviewed the proposed Prescribing Information (PI) and Medication Guide for the BLA for Stoboclo® (denosumab-xxxx) injection, for subcutaneous use (Stoboclo), proposed biosimilar to US-licensed PROLIA (denosumab) under BLA 125320.

PI and Medication Guide:

OPDP's review of the proposed Stoboclo PI is based on the draft labeling e-mailed to OPDP on October 4, 2024, and we have no comments.

A combined OPDP and Division of Medical Policy Programs (DMPP) review for the Stoboclo 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 by the sponsor to the electronic document room on September 13, 2024, 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
10/11/2024 10:52:34 AM

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

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

Memorandum

Date: October 11, 2024

To: Noreen Cabellon, Regulatory Project Manager
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 Osenvelt® (denosumab-xxxx) injection, for subcutaneous use

BLA: 761404

Background:

In response to DGE's consult request dated January 26, 2024, OPDP has reviewed the proposed Prescribing Information (PI) and carton and container labeling for the original BLA submission for Osenvelt® (denosumab-xxxx) 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 October 4, 2024, 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 September 13, 2024, 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
10/11/2024 04:13:33 PM

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM – STREAMLINED

Date:	1/24/2024		
To:	Kelly Ballard		
Requesting Center/Office:	CDER/OPQ	Clinical Review Division:	Other
From:	Tiffani Chance OPEQ/OHT3/DHT3C		
Through (Division): *optional	Shruti Mistry, Assistant Director, Injection Team OPEQ/OHT3/DHT3C		
Subject:	Consult for Submission: Review Needle Safety device system for BLA 761404		
Recommendation:	The device is pre-filled, fixed-dose and single use PFS with a safety guard. The needle safety guard uses the (b) (4), which has 510(k) clearance from CDRH. The device safety guard activation force is (b) (4) N, while the lock-out force is (b) (4) N. Testing of the relevant force attributes are performed before release. The sponsor has also applied the relevant standards (testing and biocompatibility) for the needle safety guard. Therefore, the device component is acceptable (CND).		

Digital Signature Concurrence Table

Reviewer	Team Lead (TL)	Division (optional)
Tiffani C. Chance -S Digitally signed by Tiffani C. Chance -S Date: 2024.01.24 08:55:35 -06'00'	Shruti N. Mistry -S	2024.01.24 10:28:48 -05'00'

1. SUBMISSION OVERVIEW

Table 1. Submission Information

Consult Identification #	ICCR# 00960765
Consult Request Link	https://force-dsc.lightning.force.com/lightning/r/Case/5003d00000A5ZgCAAV/view
ICC tracking #	2301133
Submission Number	BLA 761404
Sponsor	CELLTRION INC
Drug/Biologic	CT-P41
Indications for Use	CT-P41 (denosumab) is a RANK ligand (RANKL) inhibitor indicated for treatment of adult patients with the following: • Postmenopausal Women with Osteoporosis at high risk for fracture • Increase Bone Mass in Men with Osteoporosis • Glucocorticoid-Induced Osteoporosis • Bone Loss in Men Receiving Androgen Deprivation Therapy for Prostate Cancer

	• Bone Loss in Women Receiving Adjuvant Aromatase Inhibitor Therapy for Breast Cancer
Device Constituent	PFS
Related Files	There are no related files

2. CDRH REVIEW

ICC Review Request from CDER/OPQ, Other:	CDER requests a review of the Needle Safety Device.
Device Presentation(s) being evaluated:	PFS
Objective of this Memo:	Review Needle Safety device system for BLA 761404
Review Comments:	The device is pre-filled, fixed-dose and single use PFS with a safety guard. The needle safety guard uses the (b) (4), which has 510(k) clearance from CDRH. The device safety guard activation force is (b) (4) N, while the lock-out force is (b) (4) N. Testing of the relevant force attributes are performed before release. The sponsor has also applied the relevant standards (testing and biocompatibility) for the needle safety guard. Therefore, the device component is acceptable. The review of the PFS is deferred to CDER per ICCR agreement Do I Need to Request an Intercenter Consult (i.e., Intercenter Agreements)? (sharepoint.com).
Review Recommendation:	CND
Milestone	Filing: 01/29/2024

DEVICE DESCRIPTION

Sequence 0001; Module 3.2.R.2 Medical Device

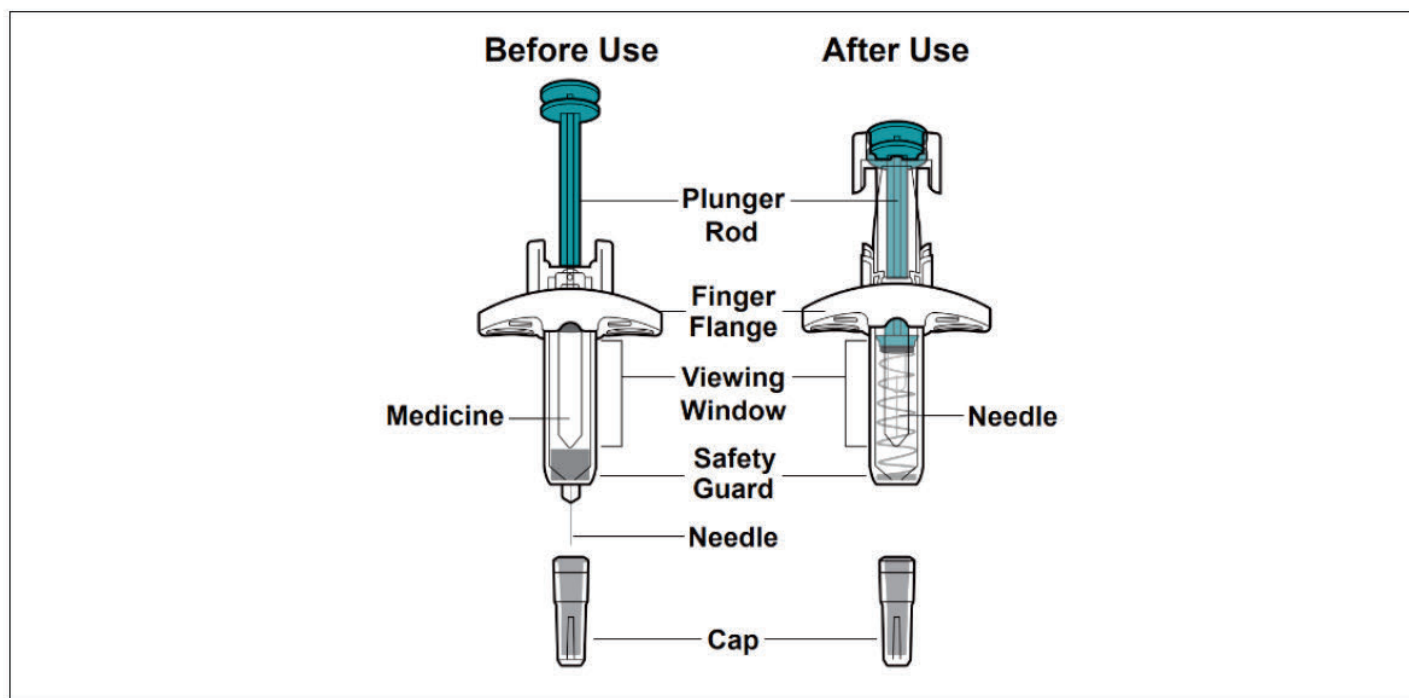


Figure 3.2.R.2-1: Operating Configuration of CT-P41 PFS-S

CT-P41 drug product is presented as pre-filled syringe with safety guard (PFS-S). The container closure system used for CT-P41 drug product is specifically designed to allow subcutaneous (SC) administration of denosumab by end users. The primary container closure system is composed of a syringe and a stopper. The syringe with staked needle is (b) (4) filled with the sterile drug product then assembled with the stopper. The secondary packaging components including a plunger rod, a finger flange and a safety guard are assembled to finalize the combination product. CT-P41 PFS-S is intended to assist healthcare professionals to deliver SC injections of CT-P41 drug product at a clinical/physician environment. The device is pre-filled, fixed-dose and single use.

Standards Followed for Pre-filled Syringe with Safety Guard (PFS-S)

- ISO 11135:2014/Amd1:2018 Sterilization of health-care products – Ethylene oxide – Requirements for the development, validation and routine control of a sterilization process for medical devices –Amendment 1: Revision of Annex E, Single batch release
- ISO 11137-1:2006/Amd 2:2018 Sterilization of health care products - Radiation – Part 1: Requirements for development, validation and routine control of a sterilization process for medical device – Amendment 2: Revision to 4.3.4 and 11.2
- ISO 11137-2:2013/Amd 1:2022 Sterilization of health care products – Radiation – Part 2: Establishing the sterilization dose — Amendment 1
- ISO 11137-3:2017 Sterilization of health care products – Radiation – Part 3: Guidance on dosimetric aspects of development, validation and routine control
- ISO 11040-4:2015 Prefilled syringes – Part 4: Glass barrels for injectables and sterilized subassembled syringes ready for filling
- ISO 11040-7:2015 Prefilled syringes – Part 7: Packaging systems for sterilized subassembled syringes ready for filling

- ISO 9626:2016 Stainless steel needle tubing for the manufacture of medical devices – Requirements and test methods
- ISO 23908:2011 Sharps injury protection – Requirements and test methods – Sharp protection features for single-use hypodermic needles, introducers for catheters and needles used for blood sampling
- ISO 10993-1:2018 Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process
- ISO 10993-2:2006 Biological evaluation of medical devices – Part 2: Animal welfare requirements
- ISO 10993-4:2017 Biological evaluation of medical devices – Part 4: Selection of tests for interactions with blood
- ISO 10993-5:2009 Biological evaluation of medical devices – Part 5: Tests for in vitro cytotoxicity
- ISO 10993-7:2008/Amd 1:2019 Biological evaluation of medical devices – Part 7: Ethylene oxide sterilization residuals – Amendment 1: Applicability of allowable limits for neonates and infants
- ISO 10993-10:2021 Biological evaluation of medical devices – Part 10: Tests for skin sensitization
- ISO 10993-11:2017 Biological evaluation of medical devices – Part 11: Tests for systemic toxicity
- ISO 10993-12:2021 Biological evaluation of medical devices – Part 12: Sample preparation and reference materials
- ISO 10993-18:2020 Biological evaluation of medical devices – Part 18: Chemical characterization of medical device materials within a risk management process
- ISO 10993-23:2021 Biological evaluation of medical devices – Part 23: Tests for irritation

Safety Guard

The (b) (4) safety guard system used for the CT-P41 PFS-S has 510(k) clearance from the United States Food and Drug Administration Center for Drug Devices and Radiological Health (CDRH).

EPR TESTING

Device EPRs, particularly needle safety guard activation force highlighted, are summarized below:

Table 3.2.R.2-5: Performance Tests for CT-P41 PFS-S

Test	Description	Acceptance Criteria	CT-P41 PFS-S			Results
			3P1W01S11	3P1W02S11	3P1W03S11	
Extractable Volume (Injection Volume)	To test that the PFS-S delivers the intended dose of drug product	(b) (4)	≥ 1.0 mL	≥ 1.0 mL	≥ 1.0 mL	Pass
Break Loose Force	To test initial force required to manually deliver intended dose of drug product.		Max: 7 N	Max: 6 N	Max: 6 N	Pass
Gliding Force	To test driving force required to manually deliver intended dose of drug product.		Max of average: 8 N	Max of average: 7 N	Max of average: 7 N	Pass
Activation Force	To test the force required to trigger the needle shield of the safety guard that is designed to prevent patient injury by exposed needle after injection.		Max: 11 N	Max: 11 N	Max: 11 N	Pass

Table 3.2.R.6-4: Functional Test Items for CT-P41 Drug Product [PFS] Shipping Validation

Test Item	Acceptance Criteria ¹
Break Loose and Gliding Force ^{2,3}	(b) (4)
Activation Force ³	
Lock Out Force ³	
Stopper Movement ^{2,3}	
Stopper position ²	

¹ If the acceptance criteria for release specification (Section 3.2.P.5.1 [PFS]) are revised, the revised limit will be used in the shipping validation.

² For unassembled drug product (uDP)

³ For assembled drug product (aDP) or finished drug product (fDP)

⁴ Acceptance criteria means (b) (4)

Device functionality over the shelf-life will be verified during the stability testing of CT-P41 drug product under long term (5±3°C) and accelerated (25±2 °C/60±5% RH) conditions. Shipping studies will be performed based on the above acceptance criteria/ specifications.

Lockout force is greater than double the activation force.

Sample size is n = 30 per batch for all tests, except extractable volume (n = 35).

All acceptance criteria specifications are acceptable.

CELLTRION performs final design control testing before release, while the other manufacturing firms involved perform design input/output control of device components.

BIOCOMPATIBILITY

Reviewer Comments:

The device is pre-filled, fixed-dose and single use PFS with a safety guard. The needle safety guard uses the (b) (4) which has 510(k) clearance from CDRH. The device safety guard activation force is (b) (4) N, while the lock-out force is (b) (4) N. The limit for the activation force is typically (b) (4) N, so the device activation force is acceptable. ISO 11608-5:2022 specifies that the force required to override the needle guard lockout must be at least twice the set maximum activation force, so the lock-out force is acceptable. Testing of the relevant force attributes are performed before release. .



For 100 devices tested, we would be (b) (4)% confident that the true failure rate is no greater than (b) (4)%. This model shows that smaller sample sizes increase the chance of accepting a device that has a potentially higher injury rate, even if no failures were reported. Apart from extractable volume, 90 total syringes are tested. This is acceptable, as the remaining tests related to the syringe with the NSD, which is already 510(k) cleared.

Therefore, the device component is acceptable.

The sponsor provided the following statement regarding Biocompatibility:

During the use of CT-P41 PFS-S, the user will come into direct contact with the materials of the outer parts of the PFS-S which are the safety guard, plunger rod, and finger flange. When the CTP41 PFS-S are handled as recommended, the contact is limited to the skin of the hands and the injection site. In accordance with ISO 10993-1:2018, the secondary device components of CT-P41 PFS-S (safety guard, plunger rod, and finger flange) are categorized as surface medical device contact with skin, for a limited exposure (≤ 24 hours). All biocompatibility tests for safety guard, plunger rod and finger flange were performed in accordance with ISO 10993-1:2018, ISO 10993-4:2017, ISO 10993-5:2009, ISO 10993-10:2021 and ISO 10993-23:2021. Testing according to 10993-1:2018 corresponds with testing the NSD article, and will be briefly reviewed.

For the duration of contact listed for the NSD, the correct endpoints are cytotoxicity, sensitization, and irritation of the skin. A brief review is provided below (NSD components only):

Tested item: Safety guard (b) (4)

Method: Extract (3cm²/mL). The extract was clear without any impurities.

Extract Conditions: 37C for 24 hours (less than device use). The extract was used <24h after processing.

Sensitization testing: Guinea Pig Maximization Test.

Irritation: Dermal Irritation.

Cytotoxicity: (b) (4).

The correct positive and negative controls were used for each test (positive and negative for cytotoxicity, positive historical control for sensitization, and vehicle without extract for irritation). The test article was not found to be skin irritating, sensitizing, or cytotoxic.

Reviewer Comments:

The NDS is made of (b) (4), which is excluded from testing requirements per Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process" Guidance for Industry and Food and Drug Administration Staff. A very brief summary of sponsor testing was provided above. The sponsor followed testing according to 10993-1. Therefore, the biocompatibility testing is acceptable.

STERILIZATION

(b) (4)

An absolute bioburden test is conducted to verify/ validate sterilization methods, which is acceptable.

Reviewer Comments:

(b) (4)

he methods of sterilization, as well as validation methods, are acceptable.

Therefore, sterilization methods are acceptable.

---END OF REVIEW---

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/s/

NOREEN N CABELLON
10/09/2024 12:31:11 PM
Signing on behalf of Tiffani Chance, OPEQ/OHT3/DHT3C

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:	October 1, 2024
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	BLA 761404
Product Name, Dosage Form, and Strength:	Osenvelt (denosumab- bmwo) injection, 120 mg/1.7 mL (70 mg/mL)
Applicant Name:	Celltrion, Inc. (Celltrion)
FDA Received Date:	September 13, 2024
TTT ID #:	2023-7435-3
DMEPA 1 Safety Evaluator:	Peggy Rahbani, PharmD, BCPS
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 PURPOSE OF MEMORANDUM

Celltrion, Inc. submitted revised container label and carton labeling received on September 13, 2024, for Osenvelt. The Division of General Endocrinology (DGE) requested that we review the revised container label and carton labeling for Osenvelt (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

Celltrion, Inc. implemented all of our recommendations and we have no additional recommendations at this time.

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

^a Rahbani P. Label and Labeling Review for Osenvelt (BLA 761404). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2024 Aug 27. TTT ID: 2023-7435-2.

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/s/

PEGGY M RAHBANI
10/01/2024 08:18:20 AM

YEVGENIYA M KOGAN
10/01/2024 09:57:31 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:	October 1, 2024
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	BLA 761404
Product Name, Dosage Form, and Strength:	Stoboclo (denosumab- bmwo) injection, 60 mg/mL
Applicant Name:	Celltrion, Inc. (Celltrion)
FDA Received Date:	September 13, 2024
TTT ID #:	2023-7341-3
DMEPA 1 Safety Evaluator:	Peggy Rahbani, PharmD, BCPS
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 PURPOSE OF MEMORANDUM

Celltrion, Inc. submitted revised container label and carton labeling received on September 13, 2024, for Stoboclo. The Division of General Endocrinology (DGE) requested that we review the revised container label and carton labeling for Stoboclo (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

Celltrion, Inc. implemented all of our recommendations and we have no additional recommendations at this time.

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

^a Rahbani P. Label and Labeling Review for Stoboclo (BLA 761404). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2024 Aug 27. TTT ID: 2023-7341-2.

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/s/

PEGGY M RAHBANI
10/01/2024 08:20:35 AM

YEVGENIYA M KOGAN
10/01/2024 09:58:15 AM

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:	September 26, 2024
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	BLA 761404
Product Type:	Combination Product (Biologic-Device)
Product Name, Dosage Form and Strength:	Stoboclo ¹ (denosumab-bmwo) ² injection, 60 mg/mL
Device Constituent:	Prefilled syringe (PFS)
Rx or OTC:	Rx
Applicant/Sponsor Name:	Celltrion, Inc. (Celltrion)
Submission Date:	November 30, 2023; February 9, 2024; August 13, 2024
OSE TTT #:	2023-7343
DMEPA 1 Safety Evaluator:	Lisa Huang, PharmD, MPH
DMEPA 1 Team Leader:	Murewa Oguntimein, PhD, MHS, CPH, MCHES
DMEPA 1 Associate Director for Human Factors:	Ariane O. Conrad, PharmD, BCACP, CDCES, FISMP

¹ CT-P41 has been developed as a proposed biosimilar and interchangeable biosimilar to US-licensed Prolia. The proprietary name, Stoboclo was found conditionally acceptable on February 28, 2024. For the purposes of this review, the proprietary name placeholder “CT-P41”, is used throughout the review to refer to this product.

² The nonproprietary name suffix for this BLA -“bmwo” was found conditionally acceptable on August 12, 2024.

1 REASON FOR REVIEW

On November 30, 2023, Celltrion submitted Biologics License Application (BLA) 761404 that included a comparative analysis (CA) and justification for not submitting Human Factors (HF) Validation study and Comparative Use Human Factors (CUHF) study results to support their marketing application for CT-P41 (denosumab-bmwo) injection, 60 mg/mL prefilled syringe as a proposed biosimilar and interchangeable biosimilar to US-licensed Prolia (hereafter, called Prolia).

2 BACKGROUND

CT-P41 is a single ingredient combination product with a single-dose prefilled syringe (PFS) device constituent part, intended for administration by health professionals. CT-P41 is a receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor proposed for the:

- 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 May 6, 2021, Celltrion submitted a use-related risk analysis (URRA), CA, and justification for not submitting HF validation study results under IND 147751 to support their future marketing application for CT-P41 PFS, as a proposed biosimilar to Prolia PFS. On October 21, 2021, we reviewed the URRA, CA, and justification for not submitting HF validation results. We determined Celltrion does not need to submit HF validation study results to support their future marketing application for CT-P41 PFS as a biosimilar to Prolia. We also stated that if Celltrion modified the product user interface, additional human factors considerations may apply.³

On November 30, 2023, Celltrion submitted their marketing application under BLA 761404 for CT-P41 PFS as a proposed biosimilar and interchangeable biosimilar to Prolia. This submission included a comparative analysis. However, it was not clear if the comparative analyses submitted under BLA 761404 was identical to the comparative analyses we previously reviewed under IND 147751. Additionally, it was not clear if the product user interface of the proposed CT-P41 PFS presentation submitted under BLA 761404 was identical to the product user interface of the proposed CT-P41 PFS evaluated in the URRA, CA and justification submitted on May 6, 2021, under IND 147751. Furthermore, we noted Celltrion submitted a proposed instructions for use (IFU) to be included in the carton. However, the reference product, Prolia, does not have a separate IFU as the product is administered by healthcare professionals only.

³ Adeolu, A. Use-Related Risk Analysis (URRA) and Comparative Analyses Review for CT-P41. Silver Spring (MD): FDA, CDER, OSE (US); 2021 OCT 21. IND 147751.

Additionally, Prolia's prescribing information (PI) Section 2.4 includes high-level instructions for healthcare professionals on preparation and administration of the prefilled syringe. Regarding the aforementioned differences, from a biosimilar policy perspective, the Office of Therapeutic Biologics and Biosimilars (OTBB) noted it may be confusing to include a separate IFU for a product that is administered by healthcare professionals. OTBB provided comments that were incorporated in the information requested dated August 6, 2024.

Thus, we issued the following two information requests (IR):

- On February 7, 2024, we asked Celltrion to clarify if the product user interface and CA submitted in this application is identical to the version we reviewed previously under their IND 147751.
- On August 6, 2024, we recommended Celltrion remove the separate IFU and ensure that the instructions for healthcare professionals on preparation and administration of the PFS in their PI is consistent with the corresponding text in the Prolia PI Section 2.4, except for information that is specific to their proposed product and necessary to inform safe and effective use.

Subsequently, on February 9, 2024 (hereafter, referred to as IR response 1) and August 13, 2024 (hereafter, referred to as IR response 2) respectively, Celltrion provided the following IR responses:

IR response 1 dated February 9, 2024:

"CELLTRION confirms that the product user interface of our proposed CT-P41 (denosumab) prefilled syringe with safety guard (PFS-S) (60 mg/1.0 mL) evaluated in the URR, CA, and justification submitted on May 06, 2021, is identical to the product user interface of CT-P41 (denosumab) PFS-S (60 mg/1.0 mL) submitted on November 30, 2023. CELLTRION also confirms that the URR, CA, and justification are the same" and "the product user interface of the CT-P41 PFS-S (60 mg/1.0 mL) of the proposed biosimilar in the comparative analyses submitted on May 06, 2021, under IND 147751, is identical to the product user interface of the proposed CT-P41 PFS-S (60 mg/1.0 mL) of the proposed biosimilar evaluated in the comparative analyses submitted on November 30, 2023, under BLA 761404, as there is no change in the product, user interface, and justification."

Additionally, Celltrion indicated in their response that they made the following changes to the CT-P41 CA since our May 2021 review of the URR and CA:

- In the physical comparison of the CA, changed the length of the syringe barrel from (b) (4). The rationale for the change is due to revisions in the supplier's technical drawing.
- In the physical comparison of the CA, changed the height of the plunger rod from (b) (4). The rationale for the change is due to excluding the screw part in the plunger rod measurement under the BLA, compared to including the screw part under the IND.

- In the physical comparison of the CA, changed the plunger rod pad diameter from (b) (4). Celltrion did not provide a rationale for the change; however, they stated, *“the difference of (b) (4) mm is negligible considering the measurement variance.”*

IR Response 2 dated August 13, 2024:

Regarding Celltrion’s proposed IFU and PI, Celltrion implemented our recommendations to remove their proposed IFU and align their PI section 2.3 with US-licensed Prolia PI Section 2.4. Additionally, we note that the DMEPA 1 nomenclature and labeling review team evaluated product specific label and labeling under a separate cover.⁴

Based on our independent expert review of the aforementioned information, we determined that these CA 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 biosimilar and interchangeable biosimilar product to Prolia. Therefore, we determine that these CA and labeling differences do not warrant data from a human factors validation study and comparative use human factors study.

3 CONCLUSION

Based on the aforementioned information, we determined that Celltrion does not need to submit human factors validation study and comparative use human factors study results with their marketing application for CT-P41 (denosumab-bmwo) injection, 60 mg/mL, PFS, as a proposed biosimilar and interchangeable biosimilar to Prolia. We have no HF recommendations for this marketing application.

⁴ Rahbani, P. Label and Labeling Review for Stoboclo (denosumab-xxxx) 60 mg/mL injection. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2024 FEB 26. BLA 761404.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. COMPARATIVE ANALYSES

Comparative Analyses is accessible in EDR via:

<\\CDSESUB1\EVSPROD\bla761404\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\women-osteoporosis\5354-other-stud-rep\hf-study\hf-study-and-comparative-analysis.pdf>

APPENDIX B. INFORMATION REQUESTS ISSUED DURING THE REVIEW

On February 7, 2024, we issued an information request (IR) requesting Celltrion to submit the following:

- Specify if the product user interface of your proposed CT-P41 (denosumab) 60 mg/mL PFS evaluated in the URRA, CA, and justification submitted on May 06, 2021, is identical to the product user interface of your CT-P41 (denosumab) 60 mg/mL PFS submitted on November 30, 2023. If there are any changes, please indicate what changes you made to the user interface.
- Specify if the URRA, CA, and justification evaluated in your May 06, 2021, submission is the same as the CA and justification submitted in your November 30, 2023, submission. If there are any changes, please specify the changes you made to the use-related risk analysis.

On February 9, 2024, Celltrion provided an acceptable response, that can be accessed in EDR via:

<\\CDSESUB1\EVSPROD\bla761404\0003\m5\53-clin-stud-rep\535-rep-effic-safety-stud\women-osteoporosis\5354-other-stud-rep\clinical-information-amendment\clinical-information-amendment-1.pdf>

<\\CDSESUB1\EVSPROD\bla761404\0003\m5\53-clin-stud-rep\535-rep-effic-safety-stud\women-osteoporosis\5354-other-stud-rep\clinical-information-amendment\clinical-information-amendment-1-attachment1.pdf>

On August 6, 2024, we issued an IR recommending Celltrion to:

- Remove the proposed separate IFU, as a separate IFU does not exist for the reference product, Prolia, and would be redundant with the instructions in your proposed PI Section 2.3.
- Ensure the text for your proposed PI section 2.3, instructions for healthcare professionals on preparation and administration of the prefilled syringe, is consistent with the corresponding text in the Prolia PI Section 2.4, except for information that is specific to your proposed product and necessary to inform safe and effective use.

On August 13, 2024, Celltrion provided an acceptable response, that can be accessed in EDR via:

<\\CDSESUB1\EVSPROD\bla761404\0024\m5\53-clin-stud-rep\535-rep-effic-safety-stud\women-osteoporosis\5354-other-stud-rep\hf-study\response-to-hf-information-request.pdf>

APPENDIX C. LABELS AND LABELING AND PACKAGING

C.1 List of Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,⁵ along with postmarket medication error experiences with similar products, we reviewed the following CT-P41 (denosumab-bmwo) labeling submitted by Celltrion on November 30, 2023.

Prescribing Information (Image not shown):

<\\CDSESUB1\EVSPROD\bla761404\0001\m1\us\draft-labeling-text-60mg-pfs-s.pdf>

⁵ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

LISA HUANG
09/26/2024 01:59:42 PM

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09/26/2024 03:21:43 PM

ARIANE O CONRAD
09/30/2024 08:29:58 AM

Clinical Inspection Summary

Date	September 06, 2024
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 Noreen Cabellon, Consumer Safety Officer Division of General Endocrinology (DGE)
BLA #	761404
Applicant	Celltrion Inc.
Drug	CT-P41 (denosumab); proposed biosimilar to Prolia® and Xgeva®
NME (Yes/No)	No
Review Priority	Standard
Proposed Indication(s)	For treatment of postmenopausal women with osteoporosis at high risk for fracture
Consultation Request Date	January 19, 2024
Summary Goal Date	September 29, 2024
Action Goal Date	November 29, 2024
PDUFA Date	November 29, 2024

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study **CT-P41 3.1** entitled “A Double-blind, Randomized, Active-controlled, Phase 3 Study to Compare Efficacy, Pharmacokinetics, Pharmacodynamics, and Safety of CT-P41 and US-licensed Prolia in Postmenopausal Women with Osteoporosis” were submitted in this original Biological License Application (BLA) for CT-P41 (denosumab; proposed biosimilar to Prolia® and Xgeva®) for treatment of postmenopausal women with osteoporosis at high risk for fracture. Two foreign (Poland) clinical investigators (CIs): Drs. Edward Czerwinski (Site #2509) and Krzysztof Szymanowski (Site #2510); the sponsor Celltrion, Inc. (Celltrion) and the Contract Research Organization (CRO) (b) (4) were inspected for the submitted study.

Based on the overall inspection results of the two CIs, sponsor and the CRO; and the regulatory assessments, the data generated by these CI sites and the primary efficacy endpoint data that were centrally read by the CRO; and 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; and Xgeva® 70 mg/mL injection was approved on 11/18/2010 under BLA 125320/07 for treatment of postmenopausal women with osteoporosis at high risk for fracture. Celltrion submitted an original BLA 761404 on 11/30/2023 for CT-P41, proposed biosimilar to Prolia® and Xgeva®. Data from a Phase 3 study CT-P41 3.1 was submitted to support the regulatory decision.

Study CT-P41 3.1

Study CT-P41 3.1 was a double-blind, randomized, active-controlled, Phase 3 study to compare the efficacy, pharmacokinetics, pharmacodynamics, and safety of CT-P41 and Prolia® in postmenopausal women with osteoporosis.

The primary study objective was to demonstrate the equivalence of CT-P41 to Prolia® in terms of efficacy in postmenopausal women with osteoporosis as determined by percent change from baseline in bone mineral density (BMD) for lumbar spine (L1-L4) at Week 52.

The primary efficacy endpoint was the percent change from baseline in BMD for lumbar spine (L1-L4) by dual-energy X-ray absorptiometry (DEXA) at Week 52.

Study Design:

The study consisted of a:

- **Screening Period:** 28 days prior to randomization.
- **Treatment Period I:** 52 weeks. Eligible subjects were randomized at a 1:1 ratio to receive SC injection of 60 mg of CT-P41 or Prolia® on Week 0 and Week 26. The randomization was stratified by age (< 65 years or ≥ 65 years), baseline lumbar spine BMD T-score (≤ -3.0 versus > -3.0) and prior bisphosphonates therapy.
- **Treatment Period II:** Week 52-78. Subjects who were initially randomized to Prolia® in Treatment Period I were randomly re-assigned at a 1:1 ratio to either continue receiving 60 mg SC injection of Prolia® or switch to CT-P41. Subjects who were initially randomized to CT-P41 in Treatment Period I continued their CT-P41 treatment. The second randomization was stratified by change from baseline in BMD for lumbar spine at Week 52 (≥ 3% or < 3%)
- **End of Study (EOS) Visit:** Week 78.
- All subjects also received daily supplement of 1,000 mg of elemental calcium and 400 IU vitamin D from randomization to end of study (EOS) visit.

The study screened 1238 subjects, randomized 479 (240 in CT-P41 group and 239 in Prolia® group) subjects at 20 study sites in 4 foreign countries: Estonia (4), Latvia (2), Poland (10) and Ukraine (4). The first subject was randomized on 06/17/2021 and the last subject's last visit was on 05/18/2023. A total of 422 (221 in CT-P41 group and 201 in Prolia® group) subjects completed Treatment Period I. Of the 201 subjects completed Treatment Period I on Prolia®, 100 were continued on Prolia® and 101 were switched to CT-P41. A total of 421 subjects completed Treatment Period II. The study database was locked on 07/31/2023.

III. RESULTS

1. Edward Czerwinski, M.D., Ph.D. (Site# 2509)

Krakowskie Centrum Medyczne Sp.Z.O.O.

Ul. Mikolaja Kopernika 32

Cracow, Malopolskie, 31-501

Poland

This CI was inspected on 03/18-21/2024 as a data audit for Study CT-P41 3.1. This was the first FDA inspection of Dr. Czerwinski. The inspection was aided by an independent interpreter for Polish language translation.

For the inspected study, the site screened 221 subjects, enrolled 86 subjects with 74 subjects completed the study. The first subject consented on 06/07/2021. Source records for 30 of 221 screened subjects were reviewed in detail.

The inspection reviewed the studies' protocols and amendments, Informed Consent Forms (ICFs) and versions, 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 data of the percent change from baseline in BMD for L1-L4 by DEXA at Week 52 were centrally read. The inspection verified that the procedures were done per the protocol. The reports the site received from the sponsor were reviewed with no discrepancies noted. There were no underreporting of AEs or SAEs.

There was one discussion item: Subject # (b) (6)'s (CT-P41 group)'s concomitant medication use of Pramolan (opipramol; 50 mg) for depression documented on (b) (6) in the CRF was not included in the submission.

Reviewer's Comments:

Although the medication used is not a prohibited medicine, the subject's concomitant medication use should be reported and submitted. This is an isolated finding, and it should not affect the efficacy or safety evaluation of the submitted study.

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

2. Krzysztof Szymanowski, M.D., Ph.D. (Site# 2510)

Poznanska 14

60-185 Skórzewo

Poznan
Poland

This CI was inspected on 05/13-17/2024 as a data audit for Study CT-P41 3.1. This was the first FDA inspection of Dr. Szymanowski. The inspection was aided by an independent interpreter for Polish language translation.

For the inspected study, the site screened 170 subjects and enrolled 63 subjects with 57 subjects completed the study. The first subject consented on 09/01/2021 and the last subject's last visit was on 11/16/2023. Source records for all 63 enrolled subjects were reviewed.

The inspection reviewed the studies' protocol and amendments, ICFs and versions, 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 reports 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 the percent change from baseline in BMD for L1-L4 by DEXA at Week 52 were centrally read. The inspection verified that the procedures were done per the protocol. Subjects' DEXA reports with the BMD data for primary efficacy endpoint received were reviewed with no discrepancies noted. There were no underreporting of AEs or SAEs.

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

3. CELLTRION, Inc. (Sponsor)
19F, IBS Building, 263, Central-ro
Yeonsu-gu
Incheon, 22014
Republic of Korea

The sponsor was inspected on 04/22-05/03/2024 as a data audit for Study CT-P41 3.1 of this submission combined with Postmarketing Adverse Drug Experience (PADE) inspection. The following summary covers the sponsor inspection for Study CT-P41 3.1 only. This was the second FDA inspection of the sponsor Celltrion. The previous inspection was in 04/2015 and no significant GCP issues were identified.

For Study CT-P41 3.1, the inspection reviewed the sponsor's organizational charts; approved products; contracts and oversight of the CRO (b) (4) and other vendors; clinicaltrials.gov registration; SOPs for project and vendor management/oversight; procedures for training, financial disclosure and query, database lock and study unblinding, electronic records and signature; IP management: accountability, returns, reconciliation, and destruction processes.

The inspection reviewed the sponsor's data management, transfer, and validation process with the CRO (b) (4) who was responsible for central read of BMD results by DEXA to determine the primary efficacy endpoint of the percent change from baseline in BMD for L1-L4 at Week 52. BMD data at baseline, Week 26, Week 52, and Week 78 (end of study) were verified for 6 subjects (b) (6) for Sites #2509 and #2510, with no discrepancies noted when comparing the central reads to the line listings.

The inspection also reviewed the study's Data & Safety Monitoring Board (DSMB) charter with activities and safety endpoints, including site monitoring logs and clinical trial agreement along with the CI's qualifications of the top 6 enrolling sites, and monitoring reports for Sites #2509 and #2510.

The inspection found the following deficiencies related to Study CT-P41 3.1:

- A. No specific detail or documentation was provided to confirm timely communication to the DSMB or adjudication committee; or respective IRB or IEC for the death of 2 subjects: (b) (6) (CT-P41 group) and (b) (6) (Prolia group). Subject # (b) (6)'s death of ovarian cancer on (b) (6) was informed to the site on (b) (6) but not entered into the eCRF until (b) (6). Subject # (b) (6)'s death of pancreatic cancer and coronary artery disease on (b) (6) was not entered into the eCRF by site until (b) (6).

Reviewer's Comments:

- The sponsor responded on 05/24/2024 that the two death cases were reported to the IRB/EC and were reviewed during the DSMB meeting (documents submitted), but not within 24 hours of the death. Celltrion has developed a SOP to improve the management of safety reporting and documentation process.
 - The sponsor's responses are acceptable. Although these were regulatory violations, the 2 SAEs were reported as SAE deaths in the data listing. These delayed reports of SAEs appear unlikely to affect the safety evaluation of the study.
- B. A variety of protocol deviations were found during the files review for the 2 specific sites: #2509 and #2510. Protocol deviations identified including protocol deviations related to inclusion/exclusion criteria; concomitant medications use; informed consent issues; subjects on Prolia treatment in Treatment Period I were not re-randomized in Treatment Period II per protocol (4 subjects); laboratory out-of-window (OOW) issues; study procedure deviations; labs were not reviewed in time.

Reviewer's Comments:

- The sponsor responded on 05/24/2024 and acknowledged the protocol deviations and has developed a SOP with an emphasis on site-specific measurements to improve sites oversights. The sponsor's responses are acceptable.
- The protocol deviations were at the CI sits and CI Inspections of the 2 sites verified that these protocol deviations were reported in the submission.

- C. Clinical monitoring queries remained unresolved for long time: A total of 1,463 queries required ≥ 60 days to be closed; 371 queries were pertained to AEs and 262 queries were for concomitant medications uses. The longest prolonged query resolution time was 658 days.

Reviewer's Comments:

- *The sponsor responded on 05/24/2024 and acknowledged the deficiencies in query management and has developed a plan to improve the query process.*
- *The sponsor's responses are acceptable. The finding that 1,463/81,485 (1.79%) late-closed queries are less likely to have significant impact on the efficacy or safety results of the study.*

In general, the sponsor's oversight and monitoring of Study CP-41 3.1 appear acceptable except for the deficiencies noted above.

4.  (b) (4)

This CRO was inspected on  (b) (4) as a data audit for Study CT-P41 3.1. This was the first FDA inspection of  (b) (4), at the  (b) (4) location.

For the inspected study,  (b) (4) was responsible for project management, regulatory affairs, pharmacovigilance (PVG), clinical monitoring, medical writing, quality assurance, bioanalytical analysis, and central laboratories.

The inspection reviewed the CRO's organizational charts, list of studies conducted; transfer of obligations from the sponsor; contracts with vendors; SOPs related to clinical operations, site selection, training, vendor selection and oversight, safety reporting, risk management, site monitoring and auditing, business continuity, and deviation reporting; SAEs reporting procedures and safety tracking system. In particular, site-specific study documents, including monitoring visit logs and reports, subject screening and enrollment logs, IP shipment and storage documentation, delegations of authority, financial disclosure forms for all CIs, clinical trial agreements, clinical investigator and study staff CVs; data safety monitoring board charter meeting minutes, member training and qualifications, for 5 of 20 (#2301, 2507, 3401, 3402 and 3802) sites were reviewed in detail.

In general, the CRO's management and monitoring of Study CP-41 3.1 appear adequate, 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.
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Jenn Sellers, M.D., Ph.D.
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Central Doc. Rm.\BLA 761404
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DGE\Reviewer\Olivia Easley
DGE\Project Manager\Noreen Cabellon
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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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JENN W SELLERS
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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:	August 27, 2024
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	BLA 761404
Product Name, Dosage Form, and Strength:	Osenvelt (denosumab- bmwo) injection, 120 mg/1.7 mL (70 mg/mL)
Applicant Name:	Celltrion, Inc. (Celltrion)
FDA Received Date:	June 20, 2024
TTT ID #:	2023-7435-2
DMEPA 1 Safety Evaluator:	Peggy Rahbani, PharmD, BCPS
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 PURPOSE OF MEMORANDUM

Celltrion, Inc. submitted revised container label and carton labeling received on June 20, 2024, for Osenvelt. The Division of General Endocrinology (DGE) requested that we review the revised container label and carton labeling for Osenvelt (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

Celltrion implemented most of our recommendations. However, we note that Celltrion did not implement our recommendation to remove the sequence LM000000-CA000 from the container labeling. Celltrion is upholding its stance that it is essential to maintain the LM number for internal lot control and management. Additionally, we note that the LM number has been moved next to the barcode to 'improve readability and distinguish from the lot number on the container label'. We evaluated the sponsor's response and determined that their mitigation strategy is appropriate.

The revised container label and carton labeling may be further improved from a medication error perspective for the following reasons:

- We note a conditionally acceptable nonproprietary name suffix has been approved on August 8, 2024, and the suffix placeholder "-xxxx" should be replaced with the approved suffix "bmwo".
- Upon further review we concluded that this drug is used in a healthcare setting thus it does not require end users to enter beyond used date on the carton.

3 RECOMMENDATIONS FOR CELLTRION, INC. (CELLTRION)

A. General Comments (Container Label & Carton Labeling)

- a. Replace the nonproprietary name suffix placeholder "-xxxx" with the conditionally acceptable nonproprietary name suffix "bmwo" and use the intend-to-market presentation of the nonproprietary name and suffix (font, color, etc.) so that we may adequately evaluate your labels and labeling.

B. Carton Labeling

- a. Upon further review we note that the setting of use is in a healthcare setting therefore it does not require end users to record the following:

(b) (4)

^a Rahbani P. Label and Labeling Review for Osenvelt (BLA 761404). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 20 May 2024. TTT ID: 2023-7435-1.

(b) (4)

We recommend the removal of this statement to avoid confusion and clutter.

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YEVGENIYA M KOGAN
08/27/2024 11:25:01 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)

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Date of This Review:	August 27, 2024
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	BLA 761404
Product Name, Dosage Form, and Strength:	Stoboclo (denosumab- bmwo) injection, 60 mg/mL
Applicant Name:	Celltrion, Inc. (Celltrion)
FDA Received Date:	June 20, 2024
TTT ID #:	2023-7341-2
DMEPA 1 Safety Evaluator:	Peggy Rahbani, PharmD, BCPS
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 PURPOSE OF MEMORANDUM

Celltrion, Inc. submitted revised container label and carton labeling received on June 20, 2024 for Stoboclo. The Division of General Endocrinology (DGE) requested that we review the revised container label and carton labeling for Stoboclo (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

Celltrion implemented most of our recommendations. However, we note that Celltrion did not implement our recommendation to remove the LM0000000-(b)(4)000 sequence from the small container. Celltrion is upholding its stance that it is essential to maintain the LM number for internal lot control and management. We note that the LM number has been moved next to the barcode to 'improve readability and distinguish from the lot number on the container label'. Additionally, Celltrion did not implement our recommendation to remove the pharmacode away from the barcode place holder stating that scanning confusion between the pharmacode and barcode is minimized by considering the direction in which the label is wrapped around the syringe. We evaluated the sponsor's response and determined that their mitigation strategy is appropriate.

The revised container label and carton labeling may be further improved from a medication error perspective for the following reasons:

- We note a conditionally acceptable nonproprietary name suffix has been approved on August 8, 2024, and the suffix placeholder "-xxxx" should be replaced with the approved suffix "bmwo".
- Upon further review we concluded that this drug is administered by healthcare providers only therefore it does not require end users to enter beyond used date on the carton.
- Celltrion removed the statement "(b)(4)" from the carton principal display but did not remove the same statement from the side panel.

3 RECOMMENDATIONS FOR CELLTRION, INC. (CELLTRION)

A. General Comments (Container Label & Carton Labeling)

- a. Replace the nonproprietary name suffix placeholder "-xxxx" with the conditionally acceptable nonproprietary name suffix "bmwo" and use the intend-to-market presentation of the nonproprietary name and suffix (font, color, etc.) so that we may adequately evaluate your labels and labeling.

B. Carton Labeling

- a. Upon further review we note that this drug is administered by healthcare providers only, therefore it does not require end users to record the following:

^a Rahbani P. Label and Labeling Review for Stoboclo (BLA 761404). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2024 May 20. TTT ID: 2023-7341-1.

(b) (4)

We recommend the removal of this statement to avoid confusion and clutter.

- b. The net quantity statement on the side panel is inconsistent with the net quantity statement on the PDP. Per 21 CFR 201.62 the net quantity is only required on the PDP, thus we recommend deleting the statement: “(b) (4)” from the side panel.

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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:	May 20, 2024
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	BLA 761404
Product Name, Dosage Form, and Strength:	Osenvelt (denosumab-xxxx) ^a injection, 120 mg/1.7 mL (70 mg/mL)
Applicant Name:	Celltrion, Inc. (Celltrion)
FDA Received Date:	March 29, 2024
TTT ID #:	2023-7435-1
DMEPA 1 Safety Evaluator:	Peggy Rahbani, PharmD, BCPS
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

^a Since the nonproprietary name for this BLA has not yet been determined, the nonproprietary name placeholder, denosumab-xxxx, is used throughout this review.

1 PURPOSE OF MEMORANDUM

Celltrion, Inc. (Celltrion) submitted revised container label and carton labeling received on March 29, 2024 for Osenvelt. The Division of General Endocrinology (DGE) requested that we review the revised container label and carton labeling for Osenvelt (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^b

2 CONCLUSION

Celltrion implemented most of our recommendations. We note that Celltrion did not implement our recommendation below for the carton labeling and container label for the reason provided:

- We recommend relocating the LM000000-CA000 sequence elsewhere so as to prevent confusion with the lot number on the container and the NDC number on the carton.

Celltrion states that there is enough space between LM000000-CA000 and lot number, expiration date and/or the barcode. We agree that on the carton the LM000000-CA000 sequence presents less risk of numerical confusion with the NDC due to the size of the side panel and the spacing between the barcode and the numerical sequence. We also agree that on the container labeling the LM000000-CA000 numerical sequence appears smaller in size and outside the black box containing the lot and expiration information which may help mitigate numerical confusion. However, due to the small labeling size of the container labeling we urge Celltrion to only include critical information to assure readability and prominence of such information as per 21 CFR 201.10(i).

Additionally, the Celltrion addressed the following recommendations but did not implement correlating changes accordingly on the labeling. Therefore, the container label and carton labeling are unacceptable from a medication error perspective:

- General Comments (Container Label(s) & Carton Labeling)
 - As currently presented, the established name on the carton and container is written as 'Denosumab-xxxx' with a capitalized 'D' which is inconsistent with the way it is written in the Prescribing Information 'denosumab-xxxx'

- Carton Labeling

○

(b) (4)

We have an additional recommendation:

- As currently presented, the placeholder 'xxxx' for the suffix is present as part of the nonproprietary name on the principal display panel. A distinguishable

^b Rahbani P. Label and Labeling Review for Osenvelt (BLA 761404). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2024 Feb 26. TTT ID: 2023-7435.

nonproprietary name will facilitate accurate identification of the biological product by healthcare providers and patients.

3 RECOMMENDATIONS FOR CELLTRION, INC. (CELLTRION)

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

1. Change the established name, where applicable, that includes a capitalized 'D' from 'Denosumab-xxx' to 'denosumab-xxxx' so it is consistent throughout labeling.
2. Once a nonproprietary name is found conditionally acceptable for your proposed product, revise the nonproprietary name on all labels and labeling to incorporate the FDA-designated nonproprietary name suffix throughout the labels and labeling.

B. Carton Labeling



C. Container Labeling

1. We encourage the removal of unnecessary information, such as the LM000000-CA000 sequence from the small label to assure prominence and readability of critical information (e.g., proprietary name, strength, etc.) in accordance with 21 CFR 201.10(i).

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05/21/2024 09:55:27 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)

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Date of This Review:	May 20, 2024
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	BLA 761404
Product Name, Dosage Form, and Strength:	Stoboclo (denosumab-xxxx) ^a injection, 60 mg/mL
Applicant Name:	Celltrion, Inc. (Celltrion)
FDA Received Date:	March 29, 2024
TTT ID #:	2023-7341-1
DMEPA 1 Safety Evaluator:	Peggy Rahbani, PharmD, BCPS
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

^a Since the nonproprietary name for this BLA has not yet been determined, the nonproprietary name placeholder, denosumab-xxxx, is used throughout this review.

1 PURPOSE OF MEMORANDUM

Celltrion, Inc. (Celltrion) submitted revised container label and carton labeling received on March 29, 2024 for Stoboclo. The Division of General Endocrinology (DGE) requested that we review the revised container label and carton labeling for Stoboclo (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^b

2 CONCLUSION

Celltrion implemented some of our recommendations. We note that Celltrion did not implement our recommendations below for the container label for the reasons provided:

- We recommend moving or removing the pharmacode away from the barcode place holder and present it in a size that does not compete with, distract from the presentation of other required or recommended information on the label.
- We recommend deleting the LM000000-(b)(4)000 sequence since it is not required as part of the small container label content and takes away space from other vital information or relocating it elsewhere so that the numbers are not located in close proximity to the lot number and expiration date:

Celltrion states that there is enough space between LM000000 (b)(4)000 sequence and lot number, expiration date and/or the barcode and they did not address the relocation/removal recommendation of the pharmacode. We disagree with the Sponsor rationale due to space limitations of a small label and the pharmacode and LM000000-(b)(4)000 sequence are not required and compete with critical information on the container label. We continue to recommend the removal of the pharmacode and LM000000 (b)(4)000 sequence from the container label. Additionally, per 21 CFR 201.10(i), the small label such as a syringe label is required to have the following minimum amount of information: proprietary name, established name, product strength, Identifying lot or control number, name of manufacturer, packer, or distributor, and expiration date.

Additionally, Celltrion addressed the following recommendations but did not implement correlating changes accordingly on the labeling. Therefore, the revised container label and carton labeling are unacceptable from a medication error perspective:

- General Comments (Container Label & Carton Labeling)
 - As currently presented, the established name on the carton and container is written as 'Denosumab-xxxx' with a capitalized 'D' which is inconsistent with the way it is written in the Prescribing Information 'denosumab-xxxx'
- Carton Labeling

^b Rahbani P. Label and Labeling Review for Stoboclo (BLA 761404). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2024 Feb 26. TTT ID: 2023-7341.

(b) (4)

- On the PDP the net quantity is presented three times; “
“Each carton contains one Single-dose Prefilled Syringe with safety guard”, and an image of syringe followed by a “x1”. The redundancy of the net quantity clutters the PDP and the number “1” as presented part of the statement “ competes in prominence and size with the strength, proprietary name, and established name.

We have an additional recommendation:

- As currently presented, the placeholder ‘xxxx’ for the suffix is present as part of the nonproprietary name on the principal display panel. A distinguishable nonproprietary name will facilitate accurate identification of the biological product by healthcare providers and patients.

3 RECOMMENDATIONS FOR CELLTRION, INC. (CELLTRION)

A. General Comments (Container Label & Carton Labeling)

1. Change the established name, where applicable, that includes a capitalized ‘D’ from ‘Denosumab-xxx’ to ‘denosumab-xxxx’ so it is consistent throughout labeling.
2. Once a nonproprietary name is found conditionally acceptable for your proposed product, revise the nonproprietary name on all labels and labeling to incorporate the FDA-designated nonproprietary name suffix throughout the labels and labeling.

B. Carton Labeling

(b) (4)

2. Due to the prominence and redundancy of information we recommend reducing the number of net quantity statements to one statement such as “Each carton contains one Single-dose Prefilled syringe with safety guard” and removing the statement “ located above the “See prescribing information”. We recommend assuring that the net quantity statement is away from and less prominent than the product strength such as to the bottom of the principal display panel in accordance with 21 CFR 201.15(a)(6). See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).

C. Container Labeling

1. Remove/relocate the pharmacode and the LM000000 (b) (4) 000 sequence from the small container as to prevent scanning and numerical confusion and improve readability of critical information (e.g., proprietary name, strength, etc.,).

APPENDIX A. IMAGES OF LABELS AND LABELING RECEIVED ON MARCH 29, 2024

Container Label



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05/21/2024 12:05:22 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:	February 26, 2024
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	BLA 761404
Product Name, Dosage Form, and Strength:	Osenvelt (denosumab-xxxx) ^a injection, 120 mg/1.7 mL (70 mg/mL)
Product Type:	Combination Product (Biologic-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Celltrion, Inc. (Celltrion)
FDA Received Date:	November 30, 2023
TTT ID #:	2023-7435
DMEPA 1 Safety Evaluator:	Peggy Rahbani, PharmD, BCPS
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

^a Since the nonproprietary name for this BLA has not yet been determined, the nonproprietary name placeholder, denosumab-xxxx, is used throughout this review.

1 REASON FOR REVIEW

As part of the approval process for Osenvelt (denosumab-xxxx) injection, the Division of General Endocrinology (DGE) requested that we review the proposed Osenvelt prescribing information (PI), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

BLA 761404 is a 351(k) BLA and the listed drug product is Xgeva, BLA 125320.

2 MATERIALS REVIEWED

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

N/A=not applicable for this review

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

3 CONCLUSION AND RECOMMENDATIONS

The proposed prescribing information (PI), container label, 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 in Section 4 for the Division and in Section 5 for Celltrion, Inc.

4 RECOMMENDATIONS FOR DIVISION OF GENERAL ENDOCRINOLOGY (DGE)

Table 2. Identified Issues and Recommendations for Division of General Endocrinology (DGE)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information – Section 3 Dosage Forms and Strengths and Section 16 How Supplied/Storage and Handling			
1.	The product strength is not expressed as a total quantity per total volume followed by the concentration per mL.	The product strength should be expressed as the quantity per total volume followed by the quantity per milliliter (mL) for consistency.	Add the strength in [Section 3 and Section 16] in accordance with 21 CFR 201.57 (c) (4) or 21 CFR 201.57 (c) (17)]. Revise the strength description to read “120 mg/1.7 mL (70 mg/mL)”.
2.	A description of the dosage form is not provided [e.g., clear to slightly opalescent solution].	A description of identifying characteristics of the dosage form is required per 21 CFR 201.57(c)(4)(ii) and 21 CFR 201.57(c)(17)(iii).	Provide a description of identifying characteristics of the [dosage form] in accordance with 21 CFR 201.57(c)(4)(ii) and 21 CFR 201.57(c)(17)(iii).

5 RECOMMENDATIONS FOR CELLTRION, INC

Table 3. Identified Issues and Recommendations for Celltrion, Inc (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s) and Carton Labeling			
1.	The terminology within the statement of dosage “(b) (4)” needs to be revised.	The terminology within the statement “(b) (4)” is inconsistent with the terminology in the Prescribing Information.	We recommend revising the statement to read, “Recommended Dosage: See Prescribing Information.”
2.	The format for expiration date is not defined.	Clearly defining the expiration date will minimize confusion and risk for deteriorated drug medication errors.	Identify 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

Table 3. Identified Issues and Recommendations for Celltrion, Inc (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			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 be used to separate the portions of the expiration date.
3.	The product strength is not expressed as a total quantity per total volume followed by the concentration per mL.	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. A number of overdoses have occurred with small-volume parenteral because of health care practitioner or patient confusion when determining the quantity of drug in the container. In most cases, the user noticed the quantity per milliliter or concentration (e.g., 10 mg/mL) but failed to see the net quantity (e.g., 10 mL), which often appears in a different	Express the product strength as total quantity per total volume followed by the concentration per mL [e.g., 120 mg/1.7 mL (70 mg/mL)] in accordance with USP General Chapter <7>.

Table 3. Identified Issues and Recommendations for Celltrion, Inc (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		location on the container label.	
4.	As currently presented, the established name on the carton and container is written as 'Denosumab-xxxx'	The established name 'Denosumab-xxx' on the carton and container is not consistent with the way it is written in the PI 'denosumab-xxxx'	Change the established name on the PDP and the side panel of the carton and the PDP of the container to 'denosumab-xxxx' so it is consistent throughout labeling.
5.	As currently presented, LM000000-CA000 sequence appears in close proximity to the lot number and expiration date on the container label and in close proximity to the linear barcode on the carton label.	On the container, the LM000000-CA000 sequence located in close proximity to the lot number may be confused as the lot number. On the carton, the LM000000-CA000 sequence located underneath the barcode can be confused with the NDC number.	We recommend relocating the LM000000-CA000 sequence elsewhere so as to prevent confusion with the lot number on the container and the NDC number on the carton.
Carton Labeling			
1.	Currently, the net quantity statement on the principal display panel of the carton labeling appears as '1 vial'.	Net quantity statement with a limited description on the principal display panel may result in confusion regarding the contents of the carton.	Consider revising the net quantity statement to read as "1 x 120 mg single-dose vial".
2.			

(b) (4)

Appears this way on original

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

Table 4 presents relevant product information for Osenvelt (denosumab-xxxx) injection, received on November 30, 2023, from Celltrion, Inc. Osenvelt (denosumab-xxxx) is a proposed biosimilar and interchangeable to US-licensed Reference Product, Xgeva (denosumab) BLA 125320.

Table 4. Relevant Product Information for Osenvelt (denosumab-xxxx) injection and US-licensed Xgeva		
Product Name	Osenvelt	Xgeva ^b
Initial Approval Date	N/A	June 1, 2010 (BLA 125320)
Active Ingredient	denosumab-xxxx	
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	For multiple myeloma and bone metastasis from solid tumors: 120 mg every 4 weeks. For giant cell tumor of bone and 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 single-dose vial, 1 vial per carton.	
Storage	Refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton. Do not freeze. Once removed from the refrigerator, must not be exposed to temperatures above 25°C/77°F or direct light and must be used within 30 days. Discard if not used within the 30 days. Do not use.	Refrigerate at 2°C to 8°C (36°F to 46°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.

^b Xgeva [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2020 FEB 10. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125320s201lbl.pdf

	after the expiry date printed on the label. Protect from direct light and heat. Avoid vigorous shaking.	
Container Closure	single-dose vial	

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^c along with postmarket medication error experiences with similar products, we reviewed the following Osenvelt labels and labeling submitted by Celltrion, Inc

- Container label received on November 30, 2023
- Carton labeling received on November 30, 2023
- Prescribing Information (Image not shown) received on November 30, 2023, available from <\\CDSESUB1\EVSPROD\bla761404\0001\m1\us\draft-labeling-text-120mg-vial.docx>

F.2 Label and Labeling Images

Container label



1 Page(s) of Draft Labeling has 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.

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/s/

PEGGY M RAHBANI
02/27/2024 11:37:38 AM

YEVGENIYA M KOGAN
02/27/2024 11:41:56 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:	February 26, 2024
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	BLA 761404
Product Name, Dosage Form, and Strength:	Stoboclo (denosumab-xxxx) ^a injection, 60 mg/mL
Product Type:	Combination Product (Biologic-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Celltrion Inc (Celltrion)
FDA Received Date:	November 30, 2023
TTT ID #:	2023-7341
DMEPA 1 Safety Evaluator:	Peggy Rahbani, PharmD, BCPS
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

^a Since the nonproprietary name for this BLA has not yet been determined, the nonproprietary name placeholder, denosumab-xxxx, is used throughout this review.

REASON FOR REVIEW

As part of the approval process for Stoboclo (denosumab-xxxx) injection, the Division of General Endocrinology (DGE) requested that we review the proposed Stoboclo prescribing information (PI), Medication Guide (MG), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

BLA 761404 is a 351(k) BLA and the listed drug product is Prolia, BLA 125320.

MATERIALS REVIEWED

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

N/A=not applicable for this review

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

1 CONCLUSION AND RECOMMENDATIONS

The proposed prescribing information (PI), Medication Guide (MG), container label, 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 in Section 4 for the Division and in Section 5 for Celltrion Inc. Note that DMEPA 1 is evaluating the Human Factors Use-Related Risk Analysis (URRA) and Comparative Analysis under a separate cover and based on the outcome of that review, additional label and labeling comments may be forthcoming.

RECOMMENDATIONS FOR DIVISION OF GENERAL ENDOCRINOLOGY (DGE)

Table 2. Identified Issues and Recommendations for Division of General Endocrinology (DGE)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information – Section 3 Dosage Forms and Strengths and Section 16 How Supplied/Storage and Handling			
1.	A description of the dosage form is not provided [e.g., clear to slightly opalescent and colorless solution].	A description of identifying characteristics of the dosage form is required per 21 CFR 201.57(c)(4)(ii) and 21 CFR 201.57(c)(17)(iii).	Provide a description of identifying characteristics of the single-dose prefilled syringe in accordance with 21 CFR 201.57(c)(4)(ii) and 21 CFR 201.57(c)(17)(iii).

RECOMMENDATIONS FOR CELLTRION INC

Table 3. Identified Issues and Recommendations for Celltrion Inc (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label and Carton Labeling			
1.	The format for expiration date is not defined.	Clearly defining the expiration date will minimize confusion and risk for deteriorated drug medication errors.	Identify 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

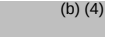
Table 3. Identified Issues and Recommendations for Celltrion Inc (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			used to represent the month. FDA recommends that a hyphen or forward slash be used to separate the portions of the expiration date.
2.	As currently presented, the established name on the carton and container is written as 'Denosumab-xxxx'	The established name 'Denosumab-xxx' on the carton and container is not consistent with the way it is written in the PI and MG 'denosumab-xxxx'	Change the established name on the carton and container to 'denosumab-xxxx' so it is consistent throughout labeling.
Container Label			
1.	As currently presented, the barcode place holder and the pharmacode on the container label are located in close proximity to each other.	The drug barcode is often used as an additional verification during the medication use process. The presence of barcodes in close proximity to one another could lead to scan errors.	We recommend moving or removing the pharmacode away from the barcode place holder and present it in a size that does not compete with, distract from the presentation of other required or recommended information on the label.
2.	As currently presented, the finished dosage form on the container is written as 'injection'	The finished dosage form 'injection' on the container is not consistent with the way it is written on the carton, in the PI, and MG 'Injection'	Change the finished dosage form on the container to 'Injection' so it is consistent throughout labeling.
3.	The manufacturer information (manufacturer name) competes in prominence with critical product information (e.g., proprietary name, established name, strength).	Critical product information such as the proprietary name, [established or nonproprietary name], and product strength should appear as the most prominent information on the principal display panel in accordance with 21 CFR 201.15.	Move the manufacturer information to the bottom of the label so it does not compete with the prominence of important product information on the principal display panel.

Table 3. Identified Issues and Recommendations for Celltrion Inc (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
4.	As currently presented the route of administration (b) (4) is not consistent with the carton label.	Inconsistent route of administration statement may lead to wrong route of administration medication errors.	We recommend revising the route of administration statement to: 'For subcutaneous use only'
5.	As currently presented, LM000000-(b) (4)000 sequence appears in close proximity to the lot number and expiration date which could lead to confusion and competes in prominence with critical product information on the label.	LM000000-(b) (4)000 sequence is not required as part of the small container label content and being located in close proximity to the lot number may be mistaken as the lot number.	We recommend deleting the LM000000-(b) (4)000 sequence since it is not required as part of the small container label content and takes away space from other vital information or relocating it elsewhere so that the numbers are not located in close proximity to the lot number and expiration date.
Carton Labeling			
1.	As presented the statement "(b) (4)" is inconsistent with the product strength of 60 mg/mL.	Inconsistent strength presentations may lead to wrong strength medication errors.	Revise "(b) (4)" should read "Stoboclo 60 mg/mL is administered once every 6 months"
2.	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 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.

Table 3. Identified Issues and Recommendations for Celltrion Inc (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
3.	(b) (4)		
4.			
4.	As presented on the back panel (b) (4) " the strength is inconsistent with the product strength of 60 mg/mL.	Inconsistent strength presentations may lead to wrong strength medication errors.	Express the product strength in accordance with USP General Chapter <7>. Revise " (b) (4) " to "60 mg/mL".
5.	The terminology within the statement "See (b) (4) for full prescribing and Manufacturing Information" is inconsistent with the terminology in the Prescribing Information and we note it is duplicative with the statement on the side panel (b) (4).	To ensure consistency with the terminology in the Prescribing Information, and to decrease clutter on the PDP.	We recommend revising the statement " (b) (4) to "prescribing information" or to delete the statement from the PDP.

Table 3. Identified Issues and Recommendations for Celltrion Inc (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
6.	On the PDP the net quantity is presented three time;  image of syringe followed by 'x1', and "Each carton contains 1 Single-dose Prefilled syringe with safety guard". The "1" in the net quantity statement, "1 single-dose Prefilled Syringe with safety guard", as well as the "x 1" that follows the graphic of the syringe compete for prominence with the strength of the product.	The redundancy in expressing net quantity is contributing to the clutter on the PDP and distracts from the important information. From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement. Product selection or dosing errors can occur if the net quantity statement is mistaken for the product strength, leading to [under- or over-dosing].	Due to the prominence and redundancy of information we recommend reducing the number of net quantity statements to one statement such as "Each carton contains 1 Sing-dose Prefilled syringe with safety guard" and changing the "1" to "one" to limit numerical confusion between strength and net quantity. We recommend assuring that the net quantity statement is away from and less prominent than the product strength, such as to the bottom of the principal display panel. See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Stoboclo (denosumab-xxxx) injection, received on November 30, 2023, from Celltrion Inc. Stoboclo (denosumab-xxxx) is a proposed biosimilar and interchangeable to US-licensed Reference Product: Prolia (denosumab) BLA 125320.

Table 4. Relevant Product Information for Stoboclo (denosumab-xxxx) injection and US-licensed Prolia		
Product Name	Stoboclo	Prolia ^b

^b Prolia [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/125320s0000lbl.pdf

Initial Approval Date	N/A	June 1, 2010
Active Ingredient	denosumab-xxxx	
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.	
Route of Administration	Subcutaneous	
Dosage Form	Injection	
Strength	60 mg/mL	
Dose and Frequency	60 mg subcutaneous injection once every 6 months	
How Supplied	Single-dose prefilled syringe with a safety guard. The prefilled syringe is not made with natural rubber latex.	60 mg/mL single-dose prefilled syringe.
Storage	Refrigerate at 2°C to 8°C (36°F to 46°F). Do not freeze. Reach room temperature (up to 25°C/77°F) in the original container prior to administration. Once removed from the refrigerator, must not be exposed to temperatures above 25°C/77°F and must be used within 30 days. If not used within 30 days, it should be discarded. 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, do not expose the product to temperatures above 25°C (77°F) and use the product within 14 days. If not used within 14 days discard the product. Protect from direct light and heat and avoid vigorous shaking.
Container Closure	single-dose prefilled syringe	

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^c along with postmarket medication error experiences with similar products, we reviewed the following Stoboclo labels and labeling submitted by Celltrion Inc.

- Container label received on November 30, 2023
- Carton labeling received on November 30, 2023
- Prescribing Information and Medication guide (Image not shown) received on November 30, 2023, available from <\\CDSESUB1\EVSPROD\bla761404\0001\m1\us\draft-labeling-text-60mg-pfs-s.pdf>

F.2 Label and Labeling Images

Container label



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

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/s/

PEGGY M RAHBANI
02/26/2024 03:29:51 PM

YEVGENIYA M KOGAN
02/26/2024 05:10:24 PM

MEMORANDUM

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

DATE: 2/21/2024

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 761404

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

Chungnam National University Hospital, Daejeon: The Office of Regulatory Affairs (ORA) conducted an inspection for the site in June 2023. The inspection was conducted under the following submission: BLA 761358.

OSIS concluded that data from the reviewed studies were reliable.

(b) (4) OSIS conducted a Remote Regulatory Assessment (RRA) for the 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.

Sites

Facility Type	Facility Name	Facility Address
Clinical	Chungnam National University Hospital (CNUH)	266 Munhwa-ro, Jung-Gu, Daejeon, South Chungcheong, Republic of Korea
Analytical	(b) (4)	

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