CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761404Orig1s000

REMS

Risk Evaluation and Mitigation Strategy (REMS) Document
STOBOCLO (denosumab-bmwo) REMS

I. Administrative Information

Risk: Severe hypocalcemia

Applicant Number: BLA 761404

Application Holder: CELLTRION, Inc.

Initial REMS Approval: 02/2025

II. REMS Goal

The goal of the STOBOCLO REMS is to mitigate the risk of severe hypocalcemia in patients with advanced chronic kidney disease (CKD), including dialysis-dependent patients, associated with STOBOCLO.

Objective 1: Inform healthcare providers on:

- Risk of severe hypocalcemia in patients with advanced chronic kidney disease (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2)
- Need to assess for presence of chronic kidney disease-mineral bone disorder (CKD-MBD) before initiating STOBOCLO in patients with advanced chronic kidney disease

III. REMS Requirements

To inform healthcare providers about the REMS and the risk and safe use of STOBOCLO, CELLTRION Inc. must disseminate REMS communication materials according to the table below:

Target Audience	Communication Materials & Dissemination Plans
Healthcare providers who are likely to prescribe STOBOCLO	REMS Letters: REMS Letter for Healthcare Providers, REMS Letter for Professional Societies with attachment Prescribing Information. 1. Mail REMS Letter for Healthcare Providers within 60 calendar days of the date STOBOCLO is first commercially distributed and again 12 months later. a. If returned, attempt to obtain updated address information and send a second letter by mail within 45 calendar days of the date the first letter is returned. If correct address cannot be obtained, the attempt will be documented. 2. Email REMS Letter for Professional Societies within 60 calendar days of the date STOBOCLO is first commercially distributed and again 12 months later through the following professional societies and request the letter or content be provided to their members. If the first email is undeliverable, the REMS letter will be mailed within 30 calendar days. If the first email is marked as unopened, a second email will be sent within 7 calendar days. If the second email is undeliverable or marked as unopened, the REMS letter will be mailed within 30 calendar days. a. American Academy of Family Physicians b. American Association of Clinical Endocrinologists

c. American College of Physicians

d. American College of Rheumatology

e. American Society of Bone Mineral Research

f. American Society of Clinical Oncology

g. Bone Health and Osteoporosis Foundation

h. Endocrine Society

i. North American Menopause Society

3. Make available via a link from the REMS Website.

4. Disseminate through field-based sales and medical representatives from the date STOBOCLO is first commercially distributed for the duration of the REMS.

5. Disseminate and prominently display at Professional Meetings where CELLTRION, Inc. has a STOBOCLO commercial presence from the date STOBOCLO is first commercially distributed for the duration of the REMS.

Patient Guide and Prescribing Information

1. Disseminate and prominently display at Professional Meetings where CELLTRION, Inc. has a STOBOCLO commercial presence from the date STOBOCLO is first commercially distributed for the duration of the REMS.

2. Disseminate through field-based sales and medical representatives during the initial and/or follow-up discussion with healthcare providers from the date STOBOCLO is first commercially distributed for the duration of the REMS. Field-based sales and/or medical representatives to verbally review the risk messages contained in the Patient Guide and Prescribing Information during the visit with the healthcare provider.

Website

1. Make the REMS Website fully operational and all REMS materials available through the website by the date STOBOCLO is first commercially distributed.

2. Maintain the REMS Website from the date STOBOCLO is first commercially distributed for the duration of the REMS.

3. Include a prominent REMS-specific link to the REMS Website on all product websites for consumers and healthcare providers. The REMS Website must not link back to the promotional product websites.

IV. REMS Assessment Timetable

CELLTRION, Inc. must submit REMS Assessments at 18 months, 3 years, and 7 years from the date of the initial REMS approval (02/28/2025). To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 calendar days before the submission date for that assessment. CELLTRION, Inc. must submit each assessment so that it will be received by the FDA on or before the due date.

V. REMS Materials

The following materials are part of the STOBOCLO REMS:

Training and Educational Material

Patient:

1. Patient Guide

Communication Materials

2. REMS Letter for Healthcare Providers
3. REMS Letter for Professional Societies

Other Materials

4. REMS Website

VI. Statutory Elements

This REMS is required under section 505-1 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355-1) and consists of the following elements:

1. Communication Plan
2. Timetable for Submission of Assessments

STOBOCLO® Patient Guide:

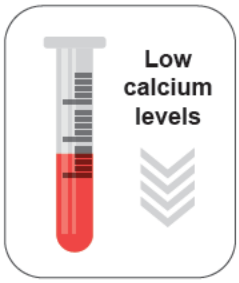
What is Stoboclo®?

Stoboclo® (denosumab-bmwo) is a prescription medicine used to:

- Treat osteoporosis (thinning and weakening of bone) in women after menopause ("change of life") who:
  - Are at high risk for fracture (broken bone)
  - Cannot use another osteoporosis medicine or other osteoporosis medicines did not work well
- Treat to increase bone mass in men with osteoporosis who are at high risk for fracture
- Treat bone loss in men who are at high risk for fracture receiving certain treatments for prostate cancer that has not spread to other parts of the body
- Treat bone loss in women who are at high risk for fracture receiving certain treatments for breast cancer that has not spread to other parts of the body
- Treat osteoporosis in men and women who will be taking corticosteroid medicines (such as prednisone) for at least 6 months and are at high risk for fracture

What is the serious risk of Stoboclo®?

Patients with advanced chronic kidney disease, including dialysis-dependent patients, are at risk of severe hypocalcemia (low calcium levels in your blood) following Stoboclo® administration.



Most people with low blood calcium levels do not have symptoms, but some people may have symptoms which include:

- Spasms, twitches, or cramps in your muscles
- Numbness or tingling in your fingers, toes, or around your mouth

Call your doctor right away if you think you may be having any of these symptoms.

What to expect before and during Stoboclo® treatment:

- Talk to your doctor before starting Stoboclo®.
- If you have low blood calcium before you start receiving Stoboclo®, it may get worse during treatment.
- Your low blood calcium must be treated before you receive Stoboclo®.
- Your doctor may prescribe calcium and vitamin D to help prevent low calcium levels in your blood while you take Stoboclo®. Take calcium and vitamin D as your doctor tells you to.
- If you have advanced chronic kidney disease (may or may not be on kidney dialysis), Stoboclo® may increase your risk for severe low calcium levels in your blood, leading to hospitalization, life-threatening events, and death.
- A mineral and bone disorder associated with kidney disease called chronic kidney disease-mineral bone disorder (CKD-MBD) may increase your risk for severe low calcium levels in blood. Before you start Stoboclo® and during treatment, your doctor may need to do certain blood tests to check for CKD-MBD.

If you have advanced chronic kidney disease, your doctor may coordinate your Stoboclo® treatment with a healthcare provider with expertise in CKD-MBD.

Reference ID: 5540405

STOBOCLO® REMS

FDA Required REMS Safety Information / Important Safety Update

Dear Healthcare Provider:

The FDA has required this safety update as part of the Stoboclo® REMS (**R**isk **E**valuation and **M**itigation **S**trategy) to inform healthcare providers about the following **serious risk of Stoboclo®**.

Severe Hypocalcemia in Patients with Advanced Kidney Disease

Patients with advanced chronic kidney disease (eGFR < 30 mL/min/1.73 m^2), including dialysis-dependent patients, are at greater risk of severe hypocalcemia following Stoboclo® administration.

- Severe hypocalcemia resulting in hospitalization, life-threatening events and fatal cases have been reported.
- To minimize the risk of hypocalcemia in patients with advanced chronic kidney disease (CKD):
  - Evaluate for the presence of chronic kidney disease-mineral bone disorder (CKD-MBD) with intact parathyroid hormone (iPTH), serum calcium, 25(OH) vitamin D, and 1,25 $(OH)_2$ vitamin D prior to decisions regarding Stoboclo® treatment.
  - Consider assessing bone turnover status (serum markers of bone turnover or bone biopsy) to evaluate the underlying bone disease that may be present.
  - Monitor serum calcium weekly for the first month after Stoboclo® administration and monthly thereafter.
  - Coordinate care with healthcare providers with expertise in CKD-MBD for patients with advanced chronic kidney disease.

Role of the Healthcare Provider

- **Provide** each patient with a copy of the **Patient Guide**.
- **Review** information in the **Patient Guide** with each patient, including the serious risk of Stoboclo® and the symptoms of severe hypocalcemia.
- **Advise** each patient to seek prompt medical attention if they have signs or symptoms of severe hypocalcemia.

This letter does not contain the complete safety profile for Stoboclo®.
Please review the Prescribing Information enclosed.

All Stoboclo® REMS materials are also available at www.stoboclorems.com.

Reporting Adverse Events
To report Adverse Reactions with Stoboclo®, please call CELLTRION USA, Inc. at 1-800-560-9414, or report the event at FDA MedWatch.

Sincerely,

CELLTRION USA, Inc.
1 Evertrust Plaza Suite 1207
Jersey City, NJ 07302

STOBOCLO® REMS

FDA Required REMS Safety Information / Important Safety Update

Dear [Professional Society]:

The FDA has required CELLTRION USA, Inc. to distribute this safety update to your organization as part of the Stoboclo® REMS (**R**isk **E**valuation and **M**itigation **S**trategy) program. We request that you inform your members about the following **serious risk of Stoboclo®**.

Severe Hypocalcemia in Patients with Advanced Kidney Disease

Patients with advanced chronic kidney disease (eGFR < 30 mL/min/1.73 m^2), including dialysis-dependent patients, are at greater risk of severe hypocalcemia following Stoboclo® administration.

- Severe hypocalcemia resulting in hospitalization, life-threatening events and fatal cases have been reported.
- To minimize the risk of hypocalcemia in patients with advanced chronic kidney disease (CKD):
  - Evaluate for the presence of chronic kidney disease-mineral bone disorder (CKD-MBD) with intact parathyroid hormone (iPTH), serum calcium, 25(OH) vitamin D, and 1,25 $(OH)_2$ vitamin D prior to decisions regarding Stoboclo® treatment.
  - Consider assessing bone turnover status (serum markers of bone turnover or bone biopsy) to evaluate the underlying bone disease that may be present.
  - Monitor serum calcium weekly for the first month after Stoboclo® administration and monthly thereafter.
  - Coordinate care with healthcare providers with expertise in CKD-MBD for patients with advanced chronic kidney disease.

Role of the Healthcare Provider

- **Provide** each patient with a copy of the **Patient Guide**.
- **Review** information in the **Patient Guide** with each patient, including the serious risk of Stoboclo® and the symptoms of severe hypocalcemia.
- **Advise** each patient to seek prompt medical attention if they have signs or symptoms of severe hypocalcemia.

This letter does not contain the complete safety profile for Stoboclo®.
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To report Adverse Reactions with Stoboclo®, please call CELLTRION USA, Inc. at 1-800-560-9414, or report the event at FDA MedWatch.

Sincerely,

CELLTRION USA, Inc.
1 Evertrust Plaza Suite 1207
Jersey City, NJ 07302

STOBOCLO® (denosumab-bmwo)

Risk Evaluation and Mitigation Strategy

What is the Stoboclo® (denosumab-bmwo) REMS?

A REMS (Risk Evaluation and Mitigation Strategy) is a program required by the Food and Drug Administration to manage known or potential serious risks associated with a drug product.

The purpose of the Stoboclo® (denosumab-bmwo) REMS is to inform healthcare providers and patients about the following serious risk of:

- Severe Hypocalcemia in Patients with Advanced Kidney Disease

The Stoboclo® (denosumab-bmwo) REMS program materials are designed to inform health providers and patients about this risk with Stoboclo® (denosumab-bmwo). The Stoboclo® REMS program materials include a REMS Letter for Healthcare Providers and a Patient Guide. It is important that you discuss with each patient the information included in the Patient Guide.

To learn more about the serious risk of Stoboclo®, read the Important Safety Information provided in this link and use the links on the right to access REMS supporting materials.

Reporting Adverse Events

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088. Healthcare providers should report all suspected adverse events associated with Stoboclo® to the FDA or to Celltrion USA at 1-800-560-9414.

MATERIALS FOR HEALTHCARE PROVIDERS

REMS Letter for Healthcare Providers

Patient Guide

Prescribing Information

MATERIALS FOR PATIENTS

Patient Guide

CELLTRION USA

Reference ID: 5540405

STOBOCLO® (denosumab-bmwo)

Risk Evaluation and Mitigation Strategy

Contact

If you have a question about the REMS, clinical inquiry or would like to report an adverse event related to Stoboclo® (denosumab-bmwo), connect online or call 1-800-560-9414.