CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761436Orig1s000
761436Orig2s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF CARDIOLOGY, HEMATOLOGY, ENDOCRINOLOGY, AND NEPHROLOGY
DIVISION OF GENERAL ENDOCRINOLGY

NDA/BLA #s: 761436
Products: Bosaya (denosumab- kyqq), injection
APPLICANT: Biocon Biologics Inc.
FROM: Marina Zemskova, M.D., Deputy Director for Safety
DATE: 9/15/2025

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;

(B) The seriousness of the disease or condition that is to be treated with the drug;

(C) The expected benefit of the drug with respect to such disease or condition;

(D) The expected or actual duration of treatment with the drug;

(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;

(F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for Bosaya to ensure that the benefits of the drug outweigh the risks of severe hypocalcemia in patients with advance chronic kidney disease (CKD) including dialysis-dependent patients. In reaching this determination, we considered the following:

A. In the United States, the age-adjusted prevalence of osteoporosis at either the femur neck or lumbar spine or both among adults aged 50 and over is 12.6% and the prevalence of low bone mass, a precursor of osteoporosis, at either the femur neck or lumbar spine or both among adults aged 50 and over is 43.1%. This estimate is based on data from National Health and Nutrition Examination Survey (NHANES), 2017-2018[1]. CKD is a risk factor for osteoporosis. Among the NHANES III participants, osteoporosis was twice as common in those with eGFR < 60 mL/min than those with eGFR > 60 mL/min[2].

B. Osteoporosis is a bone disease defined by low bone mass and skeletal fragility that predisposes patients to risk of vertebral and nonvertebral fractures. Fracture, predominantly hip fracture, is associated with loss of mobility and increased. mortality. There are multiple factors that can contribute to fractures in patients with advanced CKD. In addition to age-related or other comorbid conditions-related bone loss and/or osteoporosis, CKD patients also have alterations in vitamin D and mineral metabolism. CKD-mineral bone disease (MBD) is a distinct syndrome encompassing mineral, bone, and calcific cardiovascular abnormalities that develop as a complication of CKD. Both age-related osteoporosis and CKD-MBD can lead to increased bone fragility and fracture. Fragility fractures due to osteoporosis and/or mineral and bone disorders associated with CKD-MBD comorbidity can decrease quality of life and increase overall mortality risk in this population.

C. Bosaya is an interchangeable biosimilar product to Prolia (denosumab). Denosumab is a human monoclonal IgG2 antibody that targets the receptor activator of nuclear factor kappa B ligand (i.e., RANKL). Inhibition of RANK ligand binding to the RANK receptor underlies the efficacy of Prolia in treating all conditions for which it is indicated. Bosaya has the same mechanism(s) of action, route of administration, dosage form, strengths, and conditions of use as those of Prolia. Since Bosaya shares the same mechanism of action (i.e., functions as a RANKL inhibitor), efficacy across indications is extrapolated for Bosaya. Denosumab has demonstrated effects on fracture risk and bone mineral density in multiple osteoporosis populations, including patients with CKD stages 1-3. Although the direct evidence of fracture risk reduction in advanced and dialysis-dependent CKD patients is limited (dialysis-dependent CKD patients were excluded and only small number of patients with advanced CKD were included in the denosumab clinical trials), denosumab's benefit in advanced CKD patients is expected based on the mechanism of action. Ability to identify patients who are likely to benefit from denosumab remains difficult given the challenges with determining the pathophysiology of altered bone metabolism in advanced and dialysis-dependent CKD patients.

D. The drug will be used chronically.

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[1] Neda Sarafrazi, Ph.D., Edwina A. Wambogo, Ph.D., M.S., M.P.H., R.D., and John A. Shepherd, Ph.D. Osteoporosis or Low Bone Mass in Older Adults: United States, 2017–2018. NCHS Data Brief No. 405, March 2021.

[2] Nickolas T.L., McMahon D.J., Shane E. Relationship between moderate to severe kidney disease and hip fracture in the United States. J. Am. Soc. Nephrol. 2006;17:3223–3232

E. Bosaya is highly similar to Prolia (see above) and is expected to have the same safety profile as Prolia. Denosumab-induced inhibition of bone resorption potentially impacts the contribution of exchangeable bone calcium to the overall calcium hemostasis, thereby affecting serum calcium levels and hypocalcemia is a well-recognized consequence of anti-resorptive therapy. In addition to hypocalcimia, denosumab has been associated with osteonecrosis of the jaw, atypical femur fracture, serious infections and dermatologic reactions. Prolia was approved with REMS (June 1, 2010) to mitigate the risks of hypocalcemia, osteonecrosis of the jaw, atypical femur fracture, serious infections and dermatologic reactions. Recently, a new safety signal of severe hypocalcimia in patients with advanced CKD including dialysis-dependent patients was identified (based on postmarketing safety data and the results of Centers for Medicare and Medicaid Services (CMS) studies conducted by FDA), therefore on November 7, 2023 SLC was issued for Prolia. In addition, DGE reviewed 8-year postmarketing safety data and concluded that the incidence rates of risk of other than hypocalcemia adverse events of special interest including osteonecrosis of the jaw, atypical femoral fractures, serious infections and dermatologic reactions were stable, had no impact on the benefit risk profile of Prolia and can be adequately mitigated through labeling. Based on the above findings, DGE and OSE determined that Prolia REMS must be modified to mitigate the risk of the new safety information of severe hypocalcimia in patients with advanced CKD and that the risks of hypocalcimia, osteonecrosis of the jaw, atypical fractures, serious infections and dermatologic reactions should be removed from the REMS.

F. Bosaya not a new molecular entity.
There are several FDA-approved treatment options in multiple drug classes for osteoporosis. However, there are limited data to support efficacy of these treatments in patients with advanced or dialysis dependent CKD. Treating bone disease in patients with advanced and dialysis dependent CKD is challenged by the difficulty in diagnosis and confirmation of altered bone metabolism responsible for the low bone mass and increased fracture risk; the variability of individual patient's underlying condition and risk factors; and the complex benefit-risk considerations of any of the approved osteoporosis treatments in this population. Use of any available therapy in this population requires careful individual consideration of benefit-risk, given the patient's specific medical history and risk factors. There is unmet medical need for safe and effective therapies that reduce fracture risk for dialysis-dependent and advanced CKD patients.

The elements of the REMS will be Communication Plan (CP) and a timetable for submission of assessments of the REMS.

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/s/

MARINA ZEMSKOVA
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Division of Risk Management (DRM)
Division of Mitigation Assessment and Medication Error Surveillance (DMAMES)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number(s)	761436
Goal Date (internal)	September 16, 2025
Nexus TTT #	2024-10885
Reviewer Name	Brian Caruth, Pharm.D., BCPS
	Yanick Elame, Pharm.D. (DMAMES)
Team Leader	Yasmeen Abou-Sayed, Pharm.D.
	Kathryn Marwitz, Pharm.D., MPH (DMAMES)
Associate Director	Page Crew, Pharm.D., MPH, BCPS (DMAMES)
	Suzanne Robottom, Pharm.D.
Review Completion Date	September 12, 2025
Subject	Evaluation of proposed REMS
Trade Name	Bosaya
Established Name	Denosumab-kyqq
Applicant	Biocon Biologics Inc.
Review Division	Division of General Endocrinology
Therapeutic Class	RANK ligand (RANKL) inhibitor
Formulation(s)	Single-dose prefilled syringe containing 60 mg in a 1 mL solution
Dosing Regimen	60 mg every 6 months as a subcutaneous injection in the upper arm, upper thigh, or abdomen

Reference ID: 5658270

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates the proposed risk evaluation and mitigation strategy (REMS) for Bosaya (denosumab-kyqq) Biologic Licensing Application (BLA) 761436 submitted by Biocon Biologics Inc. on September 14, 2024 and last amended on July 8, 2025. Bosaya is proposed as a biosimilar product to the reference listed drug (RLD) Prolia, BLA 125320. Bosaya is under review in the Office of Therapeutic Biologics and Biosimilars (OTBB) and the Division of General Endocrinology (DGE). The Applicant is seeking approval for the following indications that are approved for the RLD:

- Treatment of postmenopausal women with osteoporosis at high risk for fractures
- Treatment to increase bone mass in men with osteoporosis at high risk for fractures
- Treatment of glucocorticoid-induced osteoporosis (GIOP) 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 non-metastatic prostate cancer
- Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer

The Prolia REMS, approved on June 1, 2010 and most recently modified on April 9, 2024 includes a communication plan (CP) and timetable for submission of assessments to mitigate the risk of severe hypocalcemia in patients with advanced chronic kidney disease (CKD), including dialysis-dependent patients associated with Prolia.

The elements of the Bosaya REMS proposed by the Applicant are the same as those for the currently approved Prolia REMS and include a communication plan and a timetable for submission of assessments.

DRM has determined that, as designed, the proposed REMS for Bosaya is adequate, and will communicate the same key risk messages as the approved Prolia REMS to achieve the same level of safety. This review also includes the Division of Mitigation Assessment and Medication Error Surveillance's (DMAMES) evaluation of the proposed REMS Assessment Plan. DMAMES found the REMS Assessment Plan as submitted on July 8, 2025 to be acceptable.

The proposed Bosaya REMS as submitted on July 8, 2025 is acceptable for approval.

1 Introduction

This review by the Division of Risk Management (DRM) evaluates the proposed risk evaluation and mitigation strategy (REMS) for Bosaya (denosumab-kyqq) biologic licenses application (BLA) 761436 to determine if the REMS achieves the same level of safety as the REMS for the reference listed drug (RLD), Prolia (denosumab), BLA 125320. The review also includes the Division of Mitigation Assessment and Medication Error Surveillance's (DMAMES) evaluation of the proposed REMS Assessment Plan. Bosaya was submitted by Biocon Biologics Inc. on September 14, 2024, last amended on July 8, 2025. This application is under review in the Office of Therapeutic Biologics and Biosimilars (OTBB) and Division of General Endocrinology (DGE). The Applicant is seeking approval for the same indications that are approved for the RLD:

- Treatment of postmenopausal women with osteoporosis at high risk for fractures
- Treatment to increase bone mass in men with osteoporosis at high risk for fractures
- Treatment of glucocorticoid-induced osteoporosis (GIOP) 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 non-metastatic prostate cancer
- Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer

The Applicant's proposed REMS consists of a communication plan (CP) and timetable for submission of assessments.

2 Background

2.1 Product Information

Denosumab is a human monoclonal IgG2 antibody that targets the receptor activator of nuclear factor kappa B ligand (i.e., RANKL). Bosaya is proposed to be available as a single-dose prefilled syringe containing 60 mg in a 1 mL solution. The recommended dose is 60 mg every 6 months as a subcutaneous injection in the upper arm, upper thigh, or abdomen. Duration of treatment with Bosaya is expected to be long term and likely administered in an outpatient setting.[a] The proposed indication, dosage, and presentation for Bosaya are the same as Prolia. In addition to Prolia, five denosumab biosimilars, BLA 761404 (Stoboclo [denosumab-bmwo]), BLA 761398 (Conexxence [denosumab-bnht]), BLA 761362 (Jubbonti [denosumab-bbdz]), BLA 761392 (Ospomyv [denosumab-dssb]), and BLA 761444 (Bildyos [denosumab-nxxp]), are also approved.

2.2 Prolia REMS

Prolia was approved with a REMS to ensure that the benefits outweighed the risk of osteonecrosis of the jaw, serious infection, and dermatologic reactions. The Prolia REMS was originally approved on June 1, 2010. The risks of hypocalcemia and atypical femur fracture were added to the REMS in 2012. The REMS has been modified fourteen times since approval, was last modified on April 9, 2024, and currently focuses only on the risk of hypocalcemia. Table 1 summarizes the currently approved REMS.

TABLE 1: SUMMARY OF APPROVED PROLIA REMS

REMS Goals	To mitigate the risk of severe hypocalcemia in patients with advanced chronic kidney disease (CKD), including dialysis-dependent patients, associated with Prolia
	To inform healthcare providers on the: • Risk of severe hypocalcemia with advanced chronic kidney disease (estimated glomerular filtration rate [eGFR] < 30 ml/min/1.73 m2) • Need to assess for presence of chronic kidney disease-mineral bone disorder (CKD-MBD) before initiating Prolia in patients with advanced chronic kidney disease
REMS Elements	Communication Plan • Patient Guide • REMS Letter for Healthcare Providers • REMS Letter for Professional Societies • REMS Website
Timetable for Submission of Assessments	18 months, 3, and 7 years from the date of the REMS modification (March 5, 2024)

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

2.3 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA 761436 relevant to this review:

- 09/14/24: BLA 761436 received for Bosaya (denosumab) with an incomplete REMS
- 02/19/25: FDA issued an Information Request (IR) to the Applicant to submit a REMS amendment to update the REMS materials with the trade name and include a REMS Supporting Document with sections for Key Risk Messages (KRM) and Key Performance Indicators (KPI)
- 02/27/25: The Applicant submitted a REMS amendment (sequence 0018) addressing FDA comments sent 02/19/25
- 06/27/25: FDA issued an Advice Letter informing the Applicant of the conditionally acceptable determination for their proposed product nonproprietary name, denosumab-kyqq
- 06/30/25: FDA issued an IR to the Applicant to submit a REMS amendment to update the REMS materials with the nonproprietary name and revise the assessment plan
- 07/08/25: The Applicant submitted a REMS amendment (sequence 0030) addressing FDA comments sent 06/30/25

3 Benefit Assessment

Biosimilarity of Bmab 1000 (denosumab-kyqq) to US sourced Prolia (US-Prolia) was evaluated in a phase 1 pharmacokinetic (PK) similarity study (Study B1000-NHV-01-G-01 [NCT05323708]) and a phase 3 comparative clinical study (Study B1000-PMO-03-G-02 [NCT05345691]).

Study B1000-NHV-01-G-01 was a 40-week, randomized, double-blind, two-arm, parallel group, single dose study in 189 health subjects (94 subjects in the Bmab 1000 group and 95 subjects in the US-Prolia group) 28 to 55 years of age. Subjects were randomized to receive a 60 mg subcutaneous dose of either Bmab 1000 (denosumab-kyqq) or US-Prolia. The primary outcome measures in study B1000-NHV-01-G-01 were achieved for all three PK parameters and are summarized in Table 2.

TABLE 2: SUMMARY OF PRIMARY OUTCOME MEASURES IN STUDY B1000-NHV-01-G-01

Outcome Measure (Measure Description)	Treatment Comparison and Similarity Criterion (90% Confidence Interval [CI] of the Geometric Least Squares [LS] Mean Ratios [0.80, 1.25])
	Bmab 1000 and US-Prolia
AUC_{inf} Area under the concentration-time curve from time zero to infinity	(1.06, 1.24)
AUC_{last} Area under the concentration-time curve from time zero to the last quantifiable concentration	(1.06, 1.24)
C_{max} Maximum serum concentration	(1.03, 1.19)

Source: FDA Analysis of Study B1000-NHV-01-G-01, Biosimilar Multidisciplinary Evaluation and Review, Table 6

Five subjects (three subjects in the Bmab 1000 and two subjects in the US-Prolia group) with missing data were not included in the analysis of Study B1000-NHV-01-G-01. Pharmacodynamic (PD) data was not used to assess biosimilarity, however the clinical pharmacology reviewer evaluated the PD data to ensure that it did not conflict with the PK data.

Study B1000-PMO-03-G-02 was a 78-week, randomized, double-blind, parallel group, multicenter, equivalence study in 479 female subjects with postmenopausal osteoporosis 55 to 80 years of age. Subjects were randomized to receive a 60 mg subcutaneous dose of either Bmab 1000 or US-Prolia at week zero and week 26 (main period). At week 52, subjects who had received US-Prolia were randomized again to either continue US-Prolia or were transitioned to Bmab 1000 (transition period). Subjects who had received Bmab 1000 continued to receive Bmab 1000 and followed the randomization procedure to maintain blinding. The demographics and disease characteristics were balanced between the treatment groups. The primary efficacy endpoint in study B1000-PMO-03-G-02, the percent change from baseline in lumbar spine (LS) bone mineral density (BMD) at week 52 between the Bmab 1000 and US-Prolia treatment groups was met. The difference in the mean percentage change from baseline in LS-BMD was 0.39 (90% CI [-0.22, 0.99]), when testing non-inferiority, and 0.63 (90% CI [-0.02, 1.23]), when testing non-superiority, and was within the prespecified margin (90% CI [-1.45, 1.45]).

The clinical review team concluded that biosimilarity was established between Bmab 1000 (denosumab-kyqq) and US-Prolia. This determination relied on the pre-specified PK parameter results from study B1000-NHV-01-G-01 and additional PK data from study B1000-PMO-03-G-02.

4 Risk Assessment & Safe-Use Conditions

The primary safety review of Bmab 1000 relies on data from study B1000-PMO-03-G-02 that evaluated Bmab 1000 in female subjects with postmenopausal osteoporosis. A total of 478 subjects were included in the study B1000-PMO-03-G-02 dataset (238 subjects from the Bmab 1000 group and 240 subjects from the US-Prolia group). One subject in the US-Prolia group never received a dose of study drug (withdrew consent) and was not included in the dataset. The clinical reviewer focused on study B1000-PMO-03-G-02 rather than the smaller, single dose, PK similarity study (study B1000-NHV-01-G-01). Safety data from study B1000-NHV-01-G-01 that evaluated Bmab 1000 in healthy subjects was examined for known risks of denosumab.

There were no deaths reported in study B1000-NHV-01-G-01. One death was reported in study B1000-PMO-03-G-02 in a subject randomized to US-Prolia. The death (cerebrovascular accident) was not attributed to Bmab 1000.

There was a slight excess in serious adverse events (SAEs) that occurred in subjects in the Bmab 1000 treatment group (14/238 [5.9%]) compared to subjects in the US-Prolia treatment group (7/240 [2.9%]) during the main period and appeared to be related to a higher incidence of new malignancies in the Bmab 1000 treatment group. Four subjects in the Bmab 1000 treatment group reported a serious adverse event (SAE) of fracture (lumbar vertebral fracture, thoracic vertebral fracture, hand fracture, and foot fracture). In the transition period, two subjects reported an SAE of fracture (spinal compression fracture and radius fracture).

TEAEs that occurred in ≥ 3% of subjects in either treatment group are listed in Table 3.

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TABLE 3: TREATMENT EMERGENT ADVERSE EVENTS IN STUDY B1000-PMO-03-G-02

Main Period	Transition Period
Nasopharyngitis	Nasopharyngitis
Bacterial Infection	Bacterial Infection
Viral Infection	Viral Infection
Arthralgia	Arthralgia
Renal and Urinary Tract Infection	
Back Pain	
Lipid Disorder	
Arthritis	
Dizziness	
Headache	
Systemic Hypertension	
Hyperglycemia	
Rash	

Source: Clinical reviewer generated report

The incidence of anti-drug antibodies (ADAs) was high but comparable between the treatment groups in study B1000-PMO-03-G-02. All five TEAE related to hypersensitivity occurred in subjects in the US-Prolia group during the main period. All five subjects were positive for ADAs. No TEAEs related to hypersensitivity were reported during the transition period. The incidence of neutralizing antibodies (NAbs) was infrequent in both treatment groups (7/238 [3%] in Bmab 1000 and 5/240 [2%] in US-Prolia) during the main period.

The clinical reviewer determined that there were no significant patterns in the SAEs reported in study B1000-PMO-03-G-02 that indicated a potential safety signal. TEAEs were largely consistent with the known safety profile of denosumab. There was no meaningful difference between treatment groups throughout study B1000-PMO-03-G-02 with respect to immunogenicity data (ADAs and NAbs).

4.1 HYPOCALCEMIA

Hypocalcemia, especially in patients with bone-mineral disorder, is a known risk for denosumab. The risk is highlighted in the US-Prolia prescribing information as a boxed warning. Hypocalcemia during study B1000-NHV-01-G-01 was mild, transitory, and asymptomatic. No TEAEs related to hypocalcemia were reported and no calcium levels were below 8 mg/dL. Hypocalcemia was rare during study B1000-PMO-03-G-02. The lowest calcium level reported during the main period was 8.3 mg/dL and all subjects were asymptomatic on the day of their low calcium reading. In study B1000-PMO-03-G-02, the median change from baseline in serum calcium was comparable in both treatment groups at all subsequent measurements following study drug administration during the main period and transition period.

5 Expected Postmarket Use

The prescriber and patient population for Bosaya are expected to be similar to that of Prolia. Bosaya is likely to be prescribed in an outpatient setting by primary care providers, endocrinologists, rheumatologists, and gynecologists familiar with osteoporosis therapy. Prescribers are expected to be familiar with the known risks of RANKL inhibitor therapy. Patients with advanced chronic kidney disease who are at greater risk for severe hypocalcemia are expected to receive coordinated care from prescribers who are familiar with chronic kidney disease-mineral bone disorder (CKD-MBD) to ensure appropriateness of therapy with Bosaya.

6 Review of the Proposed REMS

The proposed REMS submitted on September 14, 2024, last amended on July 8, 2025 includes a communication plan (CP) and timetable for submission of assessments.

6.1 REMS Goals

The proposed goals for the REMS for Bosaya are the same as the RLD found in Table 1.

Reviewer Comment: *The proposed goals are acceptable.*

6.2 REMS Requirements

The proposed elements for Bosaya are the same as the currently approved REMS for the RLD and are found in Table 1. The proposed REMS materials are similar to the currently approved REMS for the RLD and include a:

- Patient Guide
- REMS Letter for Healthcare Providers
- REMS Letter for Professional Societies
- REMS Website

The REMS, as designed, will achieve the same level of safety as the REMS for the RLD as explained in detail in sections 7 through 10 below.

Reviewer Comment: *We find the REMS requirements acceptable.*

7 Timetable for Submission of Assessments

The Applicant must submit REMS assessments at 18 months, 3 years, and 7 years from the date of initial approval of the REMS.

Reviewer Comment: *The timetable for submission of assessments is the same as the RLD REMS. We find the timetable for submission of assessments acceptable.*

8 Supporting Document

The REMS Supporting Document contains the REMS program background information and a description of the operations of the REMS, including the details of the specifics of the distribution plan for the communication plan materials and included contingencies for undeliverable mail and email. The Applicant clarified how the REMS will operate, be assessed, and monitored to ensure compliance with the REMS program.

Reviewer Comment*: The information in the REMS Supporting Document, including the contingency plan for undeliverable mail and email, is similar to the RLD REMS. We find the REMS Supporting Document acceptable.*

8.1 Key Risk Messages (KRMs)

The KRMs identify the most critical safety information that stakeholders should know about the risk and safe use behaviors to mitigate the serious risk of severe hypocalcemia in patients with advanced chronic kidney disease (CKD), including dialysis-dependent patients, associated with Bosaya. The KRMs are based on the REMS goals and objectives and guide the messaging throughout the REMS materials. The proposed KRMs are as follows:

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Healthcare Providers:

- There is a risk of severe hypocalcemia in patients with advanced chronic kidney disease (eGFR < 30 mL/min/1.73 m^2), including dialysis-dependent patients
- There is a need to assess patients for presence of chronic kidney disease-mineral bone disorder (CKD-MBD) before initiating Bosaya
- Coordinate care with health care providers with expertise in CKD-MBD for patients with advanced chronic kidney disease during treatment with Bosaya

Patients:

- There is a risk of severe hypocalcemia (low calcium in the blood) in patients with advanced chronic kidney disease, including dialysis-dependent patients

***Reviewer Comment**: The proposed KRMs are acceptable.*

8.2 Key Performance Indicator (KPI)

This section includes the KPI, KPI thresholds and supporting rationale, and what actions may be taken if the KPI thresholds are not met. The proposed KPIs for the Bosaya REMS are as follows:

REMS Objective	KPI	Thresholds
Inform healthcare providers on the: 1. Risk of severe hypocalcemia in patients with advanced chronic kidney disease 2. Need to assess for presence of chronic kidney disease- mineral bone disorder (CKD- MBD) before initiating Bosaya	% of healthcare provider knowledgeable on risk of severe hypocalcemia in patients with advanced CKD and need to assess for presence of CKD-MBD before initiating Bosaya	≥ 80% targeted knowledge threshold

***Reviewer Comment**: DRM finds the KPI acceptable. For assessments involving stakeholder knowledge surveys, the Draft Guidance for Industry: Survey Methodologies to Assess REMS Goals That Relate to Knowledge recommends that the generally accepted minimum targeted knowledge threshold for achieving understanding by stakeholders is the lower bound of the 95% confidence interval with targeted knowledge rate of 80% or higher for each REMS survey knowledge domain. KPIs at or above the target threshold indicate the REMS is functioning as designed. KPIs below the target threshold may potentially indicate that the REMS is not functioning as designed, is not meeting the objective, or requires regulatory actions. However, further investigation may be warranted to determine if other confounding factors are involved to explain the KPI results, and we will review the totality of the assessment data to inform the assessment of the goals and objectives. The targeted knowledge threshold may change with more experience with the REMS and accumulation of post-market data.*

8.3 REMS Assessment Plan

The REMS Supporting Document includes the Applicant's proposed REMS Assessment Plan. The proposed REMS Assessment Plan includes metrics on Outreach and Communication, Implementation and Operations, Knowledge, Health Outcomes and/or Surrogates of Health Outcomes, and an Overall Assessment of REMS Effectiveness. The Assessment Plan also includes metrics to inform on the KPI that may aid in determining if the REMS is operating as intended and meeting its goals and objectives.

***Reviewer Comments**: DMAMES reviewed the Applicant's February 27, 2025, submission of the REMS Assessment Plan contained within the REMS Supporting Document and provided joint comments to the Applicant in the June 30, 2025, Agency Information Request. The Applicant was provided with a redlined copy of the Assessment Plan and asked to:*

- *Revise the introductory statement of the Assessment Plan.*
- *Include a Utilization metric, to capture data on the extent of Bosaya use.*
- *Relocate section 5 of the REMS Supporting Document, "Overall Assessment of REMS Effectiveness," to the Assessment Plan and label it as an Assessment Plan metric.*
- *Update the tabular format of the Assessment Plan within the REMS supporting Document, to align with the requested changes.*

The Applicant appropriately addressed our comments in the July 8, 2025 submission. The Assessment Plan submitted on July 8, 2025, is acceptable and is included as an appendix to this review.

Of note, DMAMES did not review the Section 5 "REMS Assessment Methodology" of the REMS Supporting Document. DMAMES defers review of proposed survey methodologies until after action is taken and the REMS design is agreed upon. A recommendation to submit proposed REMS assessment methodologies for Agency review will be included in the action letter.

9 Impact of a Separate REMS on Access, Burden, and Safety

9.1 Impact on Burden for Healthcare Providers

The currently approved Prolia REMS includes a communication plan without a requirement linked to prescribing or dispensing. Potential for perceived burden or confusion for healthcare providers may result due to dissemination of a REMS Letter for Healthcare Providers provided by each approved program. To reduce potential stakeholder burden for healthcare providers that may already be familiar with the risks associated with denosumab products, the Bosaya REMS materials will communicate the same key risk messages as the Prolia REMS.

9.2 Impact on Access and Burden for Patients

Patient enrollment is not a requirement of the REMS and burden for patients is expected to be minimal. To reduce any potential burden for patients, the REMS materials and operational aspects of the proposed REMS are harmonized to the extent possible with the Prolia REMS to minimize confusion.

9.3 Impact on Safe Use of Denosumab

The proposed REMS for Bosaya will provide the same level of safety as the approved Prolia REMS and is designed to minimize burden for stakeholders. We note that Bosaya will potentially be the seventh approved denosumab product and with the approval of the REMS, dissemination of the Bosaya REMS Letter for Healthcare Providers may inform a greater number of prescribers about the risks associated with denosumab products.

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10 Discussion

The clinical review team recommends approval of Bosaya based on the efficacy and safety information provided in the application. The serious risk associated with the RLD is severe hypocalcemia in patients with advanced chronic kidney disease, including dialysis-dependent patients. Prolia is subject to a REMS to mitigate this risk. A REMS is necessary to ensure the benefits of Bosaya outweigh the risk of severe hypocalcemia in patients with advanced chronic kidney disease, including dialysis-dependent patients. The Applicant submitted the Bosaya REMS proposal on September 14, 2024 and last amended on July 8, 2025. The proposed separate REMS consists of a communication plan (CP) and timetable for submission of assessments. The elements of the proposed REMS as the same as the currently approved REMS for the RLD.

We acknowledge that approving multiple different denosumab product REMS will introduce some burden on the healthcare system, however, the burden is expected to be manageable as the requirements for each REMS program are the same. The availability of an additional safe and effective biosimilar product for patients is expected to offset the burden of having multiple REMS programs. Through regular assessments of each REMS, we will monitor these REMS programs and determine whether any modifications are needed in the future.

DRM determined that, as designed, the proposed REMS for Bosaya will achieve the same level of patient safety as the approved Prolia REMS that was last modified on April 9, 2024.

11 Conclusion & Recommendations

DMAMES reviewed the Assessment Plan and concluded that the July 8, 2025 Assessment Plan submission was acceptable. DRM finds the proposed Bosaya REMS to be acceptable and recommends approval of the REMS as submitted on July 8, 2025.

12 Appendices

12.1 Assessment Plan

The REMS Assessment Plan must include, but is not limited to, the following:

For each metric provide the two previous, current, and cumulative reporting periods (if applicable), unless otherwise noted.

Outreach and Communication:

1. REMS Communication Plan activities: (*Provide data for 18-month report only)
    a. *Number of Healthcare Providers (HCPs) (stratified by specialty) targeted by the REMS.
    b. *Number of professional societies targeted, and which professional societies reported distribution of the REMS letter to their respective members.
    c. *REMS Letters: A summary that includes the following information, stratified by distribution waves (i.e., date distributed):
        i. Total number and percentage of hardcopy **REMS Letter for Healthcare Providers** mailed, returned, and resent after obtaining correct address.

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ii. Total number and percentage of **REMS Letter for Professional Society** emails successfully delivered, opened, and unopened. Include the total number and percentage of hard copy letters mailed after undeliverable email attempts or for which the email address was unavailable.

d. Number and specialty of prescribers who received the **Patient Guide**

e. Date and name of the key scientific meetings attended and corresponding information on the REMS materials displayed and/or distributed.

Implementation and Operations:

2. Program Implementation (*Provide data for 18-month report only):
    a. *Date of first commercial availability of Bosaya
    b. *Date when the **REMS website** went live.
    c. Number of total visits and unique visits to the REMS website
    d. Number and type of REMS materials downloaded or accessed.
3. Utilization Data:
    a. Bosaya utilization information, including but not limited to indication and type of HCP (i.e., endocrinologist, general practitioner, internist, etc.)

Knowledge:

4. Evaluation of HCPs' knowledge:
    a. An evaluation of HCPs' understanding of the risk of severe hypocalcemia in patients with advanced chronic kidney disease via analysis of assessment survey results; and stratify results by HCP specialty (e.g., endocrinologist, rheumatologist, primary care provider).
    b. An evaluation of HCPs' understanding of the need to assess for presence of chronic kidney disease-mineral bone disorder (CKD-MBD) before initiating Bosaya and stratify results by HCP specialty.
    c. An evaluation of HCPs' understanding of the requirement to give each patient a copy of the **Patient Guide** via analysis of assessment survey results.

Health Outcomes and/or Surrogates of Health Outcomes:

5. Safety Surveillance:
    a. A summary and analysis of all post-marketing case reports of severe hypocalcemia associated with Bosaya, stratified by kidney function.

Overall Assessment of REMS Effectiveness

6. The requirements for assessments of an approved REMS under Section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

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12.2 REMS MATERIALS

Training and Educational Materials

Patient:

1. Patient Guide

Communication Materials

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

Other Materials

4. REMS Website

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/s/

BRIAN J CARUTH
09/12/2025 01:07:14 PM

YANICK E ELAME
09/12/2025 01:19:04 PM

YASMEEN I ABOU-SAYED
09/12/2025 03:46:27 PM

KATHRYN K MARWITZ
09/12/2025 03:48:46 PM

PAGE E CREW
09/12/2025 03:50:48 PM

SUZANNE B ROBOTTOM
09/12/2025 04:04:48 PM

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

Application Type	BLA
Application Number	761436
BsUFA Goal Date	September 16, 2025
Nexus TTT#	2024-10885
Reviewer Name(s)	Brian Caruth, Pharm.D., BCPS
Team Leader	Yasmeen Abou-Sayed, Pharm.D.
Review Completion Date	February 19, 2025
Subject	Interim Review of proposed REMS
Established Name	Denosumab
Trade Name	Bosaya
Name of Applicant	Biocon Biologics Inc.
Therapeutic Class	RANK ligand (RANKL) inhibitor
Formulation(s)	Single-dose prefilled syringe containing 60 mg in a 1 mL solution
Dosing Regimen	60 mg every 6 months as a subcutaneous injection in the upper arm, upper thigh, or abdomen

Reference ID: 5533775

TABLE OF CONTENTS

Reference ID: 5533775

1. Introduction

This review by the Division of Risk Management (DRM) evaluates the proposed REMS for Bosaya (denosumab), Biologics License application (BLA) 761436, submitted by Biocon Biologics Inc. on September 14, 2024.

Bosaya is a monoclonal antibody specific to receptor activator of nuclear factor kappa B ligand (RANKL) proposed as an interchangeable biosimilar to the United States approved Prolia, BLA 125320. The proposed indication, same as BLA 125320, for Bosaya is for:

- Treatment of postmenopausal women with osteoporosis at high risk for fractures
- Treatment to increase bone mass in men with osteoporosis at high risk for fractures
- Treatment of glucocorticoid-induced osteoporosis (GIOP) 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 non-metastatic prostate cancer
- Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer

This application is under review in the Division of General Endocrinology (DGE). This interim review includes DRM's comments on the REMS proposal.

2. Regulatory History

The following is a summary of the regulatory history relevant to this review:

- 09/14/24: BLA 761436 received for Bosaya (denosumab) with an incomplete REMS

3. Comments to the Applicant

We have the following comments on your proposed REMS, submitted on September 14, 2024. Review of the REMS proposal is ongoing; these comments should not be considered final. Submit a REMS amendment within 7 business days that addresses these comments. Include the following files submitted as separate documents in the same submission; according to the specific file formats (i.e. Tracked MS Word, Clean MS Word, PDF) listed in the Table below (File Formats for REMS Materials).

File Formats for REMS Materials

	Materials	**Required Formats**
1	REMS Document	Tracked MS Word, Clean MS Word, PDF
2	REMS Letter for Healthcare Providers	Tracked MS Word, Clean MS Word, PDF
3	REMS Letter for Professional Societies	Tracked MS Word, Clean MS Word, PDF
4	Patient Guide	Tracked MS Word, Clean MS Word, PDF
5	REMS Website	PDF
6	REMS Supporting Document	Tracked MS Word, Clean MS Word, PDF
7	Compiled REMS Document (consisting of REMS Document and appended REMS materials)	PDF

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General Comments

- Revise references to the proposed product from "Trade Name" to "Bosaya" throughout the REMS materials

REMS Document

- See redlined version of document (attached) for edits to section IV REMS Assessment Timetable and formatting changes to the layout

REMS Letter for Healthcare Providers

- In the first sentence of the letter, format "serious risk of Trade Name" to bold font
- Format the bulleted lists in each section to improve readability. See attached REMS Letter for Professional Societies Word document with tracked changes as an example.

REMS Letter for Professional Societies

- In the first sentence of the letter, replace the reference to "(b) (4)" with "Biocon Biologics Inc." and format "serious risk of Trade Name" to bold font
- Format the bulleted lists in each section to improve readability
- In the Role of the Healthcare Provider section, format the following to bold font:
    - The first word of each bulleted sentence
    - Patient Guide
    - The final three sentences beginning with "This letter does not contain the complete…"
- Replace the website placeholder text with the REMS Website address
- See redlined version of document (attached) with edits and formatting changes to the layout

Patient Guide

- Format the bulleted lists in each section to improve readability
- In the "What is the serious risk of Trade Name?" section, format "Call your doctor right away if you think you may be having any of these symptoms" to bold font

REMS Website

- Format "To learn more about the serious risk of Trade Name, read the Important Safety Information provided in this link and use the links on the right to access REMS supporting materials." to bold font

REMS Supporting Document

The REMS Supporting Document should contain the background and rationale for the Bosaya REMS, description of the stakeholder responsibilities, how they carry out those responsibilities, and how the REMS will be implemented. It should also include an Assessment Plan.

- Submit a REMS Supporting Document. Your proposed REMS is incomplete without a REMS supporting document. We refer you to the following guidance: Format and Content of a REMS Document Guidance for Industry, specifically "Section IV. Procedures" which describes the contents of a REMS supporting document.
- Include information on actions to be taken for undeliverable mails and emails to healthcare providers and professional societies, and responsibilities of the sales force liaisons in providing the Patient Guide during office visits to ensure the information in the REMS Supporting Document is consistent with the requirements in the REMS Document.
- Include the following sections for Key Risk Messages (KRMs) and Key Performance Indicators (KPIs)

1. Key Risk Messages (KRMs)

   Key Risk Messages for Bosaya for healthcare providers and patients:

   Key Risk Message for healthcare providers:

   - There is a risk of severe hypocalcemia in patients with advanced chronic kidney disease (eGFR < 30 mL/min/1.73 m^2), including dialysis-dependent patients.
   - There is a need to assess patients for presence of chronic kidney disease-mineral bone disorder (CKD-MBD) before initiating Bosaya.
   - Coordinate care with health care providers with expertise in CKD-MBD for patients with advanced chronic kidney disease during treatment with Bosaya.

   Key Risk Message for patients:

   - There is a risk of severe hypocalcemia (low calcium in the blood) in patients with advanced chronic kidney disease, including dialysis-dependent patients.

2. Key Performance Indicators (KPIs)

   The Bosaya REMS will use the following KPI and associated targeted threshold for the objective of the Bosaya REMS.

REMS Objective	KPI	Thresholds
Inform healthcare providers on the: 1. Risk of severe hypocalcemia in patients with advanced chronic kidney disease 2. Need to assess for presence of chronic kidney disease- mineral bone disorder (CKD- MBD) before initiating Bosaya	% of healthcare provider knowledgeable on risk of severe hypocalcemia in patients with advanced CKD and need to assess for presence of CKD-MBD before initiating Bosaya	≥ 80% targeted knowledge threshold

REMS Assessment Plan

- Submit a REMS Assessment Plan within the REMS Supporting Document.
- Section 505-1(g)(3) of the FD&C Act specifies that a "REMS assessment shall include, with respect to each goal in the strategy, an assessment of the extent to which the approved strategy, including the elements, is meeting the goal or whether the goal or elements should be modified."
- Because the goal of your proposed REMS is knowledge based, a survey to evaluate stakeholders' understanding of the serious risk associated with Bosaya use will serve as an important tool to assess whether the REMS is meeting its goal.
- Begin the Assessment Plan with these 2 statements verbatim, "The REMS Assessment Plan must include, but is not limited to, the following: For each metric provide the two previous, current, and cumulative reporting periods (if applicable), unless otherwise noted."

For more information on KRMs and KPIs see *Draft Guidance for Industry: Survey Methodologies to Assess REMS Goals That Relate to Knowledge*, *REMS Assessment: Planning and Reporting Guidance*, and *REMS Logic Model: A Framework to Link Program Design with Assessment*.

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/s/

BRIAN J CARUTH
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YASMEEN I ABOU-SAYED
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