CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761439Orig1/Orig2s000

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: 761439
Products: Enoby (denosumab- qbde), injection
APPLICANT: Hikma Pharmaceuticals USA Inc..
FROM: Marina Zemskova, M.D., Deputy Director for Safety
DATE: 9/18/2025

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 Enoby 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. Enoby 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. Enoby has the same mechanism(s) of action, route of administration, dosage form, strengths, and conditions of use as those of Prolia. Since Enoby shares the same mechanism of action (i.e., functions as a RANKL inhibitor), efficacy across indications is extrapolated for Enoby. 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. Enoby 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. Enoby is 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
09/18/2025 09:00:47 AM

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)	761439
Goal Date (internal)	September 27, 2025
Nexus TTT #	2024-11070
Reviewer Name(s)	Christopher Booze, PharmD (DRM)
	Yanick Elame, PharmD (DMAMES)
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Associate Director(s)	Page Crew, PharmD, MPH, BCPS (DMAMES)
	Suzanne Robottom, PharmD (DRM)
Review Completion Date	September 17, 2025
Subject	Evaluation of proposed REMS
Trade Name	Enoby
Established Name	Denosumab-qbde
Applicant	Hikma
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

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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 Enoby (denosumab-qbde), Biologic Licensing Application (BLA) 761439, submitted by Hikma on September 27, 2024 and last amended on August 12, 2025. Enoby is proposed as a biosimilar product to the reference listed drug (RLD) Prolia, licensed under BLA 125320 by Amgen Inc. Enoby 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 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

Prolia is approved with a REMS to mitigate the risk of severe hypocalcemia in patients with advanced chronic kidney disease (CKD), including dialysis-dependent patients. The Prolia REMS was approved on June 1, 2010[1] and most recently modified on April 9, 2024[2].

The applicant has proposed a REMS for Enoby that consists of a communication plan (CP) and a timetable for submission of assessments, the same elements as in the currently approved Prolia REMS.

DRM has determined that the proposed REMS for Enoby is comparable and will achieve the same level of safety as the approved Prolia REMS. The Division of Mitigation Assessment and Medication Error Surveillance (DMAMES) evaluated the proposed REMS Assessment Plan, and found the REMS Assessment Plan as submitted on August 12, 2025 to be acceptable.

The proposed Enoby REMS as submitted on August 12, 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 Enoby (denosumab-qbde), biologic licenses application (BLA) 761439, to determine if the REMS achieves the same level of safety as the REMS for the reference listed drug (RLD), Prolia (denosumab), BLA 125320.

BLA 761439 was submitted by Hikma on September 27, 2024, and the REMS was last amended on August 12, 2025. This application 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 same indications that are approved for the RLD. The Applicant's proposed REMS consists of a communication plan (CP) and a timetable for submission of assessments.

2 Background

2.1 Product Information

Denosumab is a human monoclonal antibody that targets the receptor activator of nuclear factor kappa B ligand (RANKL). Currently approved products in the US include Prolia (60 mg / 1 mL in a pre-filled syringe) and Xgeva (120 mg / 1.7 mL in a single-dose vial), both submitted under BLA 125320 by Amgen and approved in 2010. Multiple biosimilars have also been approved, and a list of approved denosumab products at the time of this review is provided in the table below.

Table 1. Approved Denosumab Products

Product	Trade Name	Date Approved	Application Number
Denosumab	Prolia (60 mg / 1 mL pre-filled syringe) Xgeva (120 mg / 1.7 mL single-dose vial)	6/1/2010[1]	BLA 125320
Denosumab-bbdz	Jubbonti (60 mg / 1 mL pre-filled syringe) Wyost (120 mg / 1.7 mL single-dose vial)	3/5/2024[3]	BLA 761362
Denosumab-dssb	Ospomyv (60 mg / 1 mL pre-filled syringe) + unbranded generic Xbryk (120 mg / 1.7 mL single-dose vial) + unbranded generic	2/13/2025[4]	BLA 761392
Denosumab-bmwo	Stoboclo (60 mg / 1 mL pre-filled syringe) Osenvelt (120 mg / 1.7 mL single-dose vial)	2/28/2025[5]	BLA 761404
Denosumab-bnht	Conexxence (60 mg / 1 mL pre-filled syringe) + unbranded generic Bomyntra (120 mg / 1.7 mL single-dose vial and pre-filled syringe) + unbranded generic	3/25/2025[6]	BLA 761398
Denosumab-nxxp	Bildyos (60 mg / 1 mL single-dose vial and pre-filled syringe) Bilprevda (120 mg / 1.7 mL single-dose vial)	8/29/2025[7]	BLA 761444
Denosumab-kyqq	Bosaya (60 mg / 1 mL pre-filled syringe) Aukelso (120 mg / 1.7 mL single-dose vial)	9/16/2025[8]	BLA 761436

Hikma has developed RGB-14 (denosumab-qbde) and is seeking approval for two drug products: RGB-14-P as an interchangeable biosimilar to Prolia (under proprietary name Enoby) and RGB-14-X as an

interchangeable biosimilar to Xgeva (under proprietary name Xtrenbo).[a] RGB-14 is under review in the Division of General Endocrinology (DGE). Hikma proposes the same indications, dosing, and dosage form for Enoby and Xtrenbo as for Prolia and Xgeva respectively.

The proposed indications[b] for Enoby are:

1. Treatment of postmenopausal women with osteoporosis at high risk for fracture
2. To increase bone mass in men with osteoporosis at high risk for fracture
3. Treatment of glucocorticoid-induced osteoporosis in men and women at high risk for fracture
4. To increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer
5. To increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer

The recommended dose for Enoby is 60mg via subcutaneous (SC) injection every 6 months[c] for all listed indications.

The proposed indications for Xtrenbo are:

1. Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors
2. 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
3. Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy

The recommended dose for Xtrenbo is 120mg via subcutaneous (SC) injection every four weeks for all listed indications. Additional 120mg doses on days 8 and 15 of the first month of therapy are recommended for giant cell tumor of bone and hypercalcemia of malignancy (indications 2 & 3 above).

Prolia is approved with a REMS to mitigate the risk of hypocalcemia in patients with advanced kidney disease. Xgeva, due to differences in patient population and the resulting benefit-risk profile, is approved without a REMS. Thus, the remainder of this REMS review will focus on the product referencing Prolia (RGB-14-P / Enoby).

2.2 PROLIA REMS

Prolia was approved in 2010 with a REMS to mitigate the risks of osteonecrosis of the jaw (ONJ), serious infections, and dermatologic reactions. The original REMS consisted of a medication guide (MG), communication plan (CP), and a timetable for submission of assessments.

The Prolia REMS has undergone several modifications since 2010. In 2012, additional risks of atypical femur fracture and hypocalcemia were included in the REMS. Notably, a major modification was

[a] Section 505-1 (a) of the FD&C Act: FDAAA factor (F): Whether the drug is a new molecular entity.

[b] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.

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

approved in March 2024[9] to remove four of the five risks and refocus the REMS solely on hypocalcemia. This was in response to a Safety Labeling Change (SLC) issued in November 2023 concerning hypocalcemia in patients with advanced kidney disease, including dialysis-dependent patients. This modification consisted of the following:

- Revised the REMS goal and risk messaging concerning hypocalcemia to specifically focus on patients with advanced kidney disease, including dialysis-dependent patients.
- Revised the REMS goal and risk messaging to remove the risks of ONJ, AFF, serious infections, and dermatological reactions.
- Removed the medication guide (MG) as an element of the REMS.

The current Prolia REMS goal is to mitigate the risk of severe hypocalcemia in patients with advanced chronic kidney disease (CKD), including dialysis-dependent patients. The REMS elements consist of a communication plan (CP) and a timetable for submission of assessments.

The CP materials consist of a Patient Guide, a REMS Letter for Healthcare Providers, a REMS Letter for Professional Societies, and a REMS Website.

2.3 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA 761439 relevant to this review:

- 09/27/2024: Applicant submitted BLA 761439 for RGB-14 as a biosimilar to Prolia and Xgeva.[10]
- 03/22/2025: DRM issued interim comments to the Applicant requesting fully formatted REMS materials.[11]
- 04/17/2025: Hikma submitted a REMS amendment including fully formatted REMS materials.[12]
- 08/05/2025: DRM issued additional comments, requesting edits to the REMS document and REMS materials.[13]
- 08/12/2025: Hikma submitted a REMS amendment addressing the agency's comments.[14]

3 Benefit Assessment

The applicant submitted two studies, a phase 1 PK/PD trial in health adult male participants (RGB-14-001), and a phase 3 comparative efficacy and safety trail in patients with postmenopausal osteoporosis (RGB-14-101, NCT# 05087030).

Trial RGB-14-001 was a multi-center, randomized, double-blind, parallel-group, single-dose trial to compare the PK/PD of a 60mg subcutaneous dose of RGB-14-X with that of Xgeva sourced from the United States. A total of 165 healthy male participants were randomized in a 1:1 ratio to receive either 60 mg RGB-14-X or 60 mg Xgeva (US).

Primary endpoints were maximum observed serum concentration (C_{max}), area under the concentration-time curve (AUC) from time 0 to the last measurable concentration ($AUC_{0\text{-}last}$), and area under the

concentration-time curve from time 0 extrapolated to infinity ($AUC_{0\text{-}inf}$). For all three primary PK endpoints, geometric means and 90% confidence intervals fell within the range of equivalence, demonstrating that RGB-14-X has similar pharmacokinetics to Xgeva. The review team agreed with the sponsor's conclusion that the results of this trial could be used to infer RGB-14-P was pharmacokinetically similar to Prolia as well.

Trial RGB-14-101 was a multi-center, randomized, double-blind trial comparing the efficacy and safety of RGB-14-P to that of US-licensed Prolia. A total of 473 patients were randomized to receive two 60mg doses, 26 weeks apart, of either RGB-14-P or US-Prolia. After one year, patients in the Prolia group were re-randomized to receive a third dose of either Prolia or RGB-14-P, while patients in the RGB-14-P group all received a third dose of RGB-14-P.

The primary efficacy endpoint was percent change from baseline in Lumbar Spine-Bone Mineral Density (LS-BMD) at week 52, and a pre-specified equivalence margin of +/- 1.45% was used to assess therapeutic similarity. There were 20 patients (8%) in the RGB-14-P arm, and 23 patients (10%) in the Prolia arm, with missing data at week 52. The missing data were imputed for all patients, after which the review team performed three different analyses of the primary endpoint: one where the imputed values for RGB-14-P were decreased by the margin (1.45%) to assess non-inferiority, one where the imputed values for RGB-14-P were increased by the margin (1.45%) to assess non-superiority, and one where the values were not adjusted at all.

The least squares mean percent change in LS-BMD for RGB-14-P was 5.25, 5.52, and 5.38 using the three methods respectively, compared to 5.03 for Prolia. The estimated difference in percent change from baseline in LS-BMD at week 52 between RGB-14-P and Prolia was 0.10 (95% CI -0.52, 0.71), 0.34 (-0.27, 0.95), and 0.22 (-0.29, 0.83) for the three methods respectively. The 95% confidence intervals were fully contained within the pre-specified equivalence margin of +/- 1.45% for all three methods of analysis, leading the review team to conclude that the products were therapeutically similar based on the primary endpoint.

Secondary endpoints to compare the pharmacodynamic effect of RGB-14-P to Prolia included percent change from baseline in total hip BMD, femoral neck BMD, and bone turnover markers (serum CTX and P1NP), and all were comparable between RGB-14-P and US-Prolia groups.[d]

4 Risk Assessment & Safe-Use Conditions

The incidence of adverse events was comparable between the RGB-14 groups and the reference product groups in both trials. There were no deaths in the phase 1 study RGB-14-001. There was one death in the phase 3 study RGB-14-101, a 64-year-old female in the Prolia group who experienced a fatal

[d] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

myocardial infarction. This patient had a history of cardiovascular disease and the death was not considered related to the drug.

In study RGB-14-001, two patients reported serious adverse events (SAE), neither of which were considered related to the drug. One patient randomized to Xgeva experienced nerve compression, and one patient randomized to RGB-14-X experienced influenza.

In study RGB-14-101, SAEs occurred in 7/242 (2.9%) patients receiving RGB-14-P and 16/231 (6.9%) patients receiving Prolia. The excess incidence of SAE in the Prolia group was driven by a higher number of cardiovascular disorders and malignancies that was attributed to chance. One patient in each group experienced a fracture, both of which occurred after mechanical falls. Both patients recovered and continued the study through completion.

Other SAEs in the RGB-14-P were adverse events that would not be unexpected in postmenopausal women, such as chronic obstructive pulmonary disease (COPD), panic attack, pneumonia, and thyroid cancer. None of the SAEs in either treatment group were considered related to study drug by the investigator.

A similar number of patients in each treatment group reported at least one treatment-emergent adverse event (TEAE); 65.3% (158/242) in the RGB-14-P group and 65.8% (152/231) in the Prolia group.

The most frequently reported adverse events included vitamin D deficiency, hypocalcemia, hyperlipidemia, viral infections, and headache. The rates of most adverse events were similar between treatment groups and consistent with the known safety profile of denosumab or were typical in this patient population.

The adverse event with the most notable disparity between groups was abdominal pain; there were 10 cases of abdominal pain reported in the RGB-14-P compared to zero in the Prolia group. However, all 10 cases were mild to moderate in severity and resolved without discontinuation of the study drug. The review team concluded differences between groups in incidence of specific adverse events, including abdominal pain, was likely due to chance.

4.1 HYPOCALCEMIA

Hypocalcemia is a known risk of denosumab, especially in patients with renal impairment.[e] The labels for Prolia and all denosumab biosimilars currently feature a boxed warning for the risk of severe hypocalcemia in patients with advanced kidney disease. If approved, the labeling for Enoby will include the same boxed warning. The boxed warning informs prescribers that:

- Patients with advanced chronic kidney disease (CKD) are at greater risk for severe hypocalcemia

[e] Section 505-1 (a) of the FD&C Act: *FDAAA factor (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.*

- Patients with chronic kidney disease-mineral bone disorder (CKD-MBD) are at a markedly increased risk
- Patients should be evaluated for the presence of CKD-MBD prior to initiating treatment
- Patients with CKD-MBD being treated with denosumab should be monitored by a provider with expertise in the management of CKD-MBD

In study RGB-14-001, there were no reported adverse events of hypocalcemia, and the incidence of hypocalcemia based on laboratory assessment was similar between the treatment groups (19.3% in the RGB-14-X group and 15.9% in the Xgeva group). No patients experienced a serum calcium below 8 mg/dL and no lab-identified cases of hypocalcemia were symptomatic or considered to be clinically significant.

The prescribing information for US-Prolia recommends monitoring serum calcium within 14 days of injection, as the nadir is expected to occur within the first two weeks following administration. Participants in study RGB-14-101 were subject to routine laboratory testing beginning at week 1 after administration.

The average change in serum calcium at week 2 was -0.2 mg/dL for both the RGB-14-P and Prolia groups. The incidence of lab-assessed hypocalcemia, defined as serum calcium below the lower limit of normal, was similar during the main period between the treatment groups. A total of 17/242 patients (7%) experienced at least one reading of hypocalcemia during the main period in the RGB-14-P group, compared to 24/231 (10.4%) in the Prolia group. One patient in the Prolia group, and no patients in the RGB-14-P group, had a calcium value below 8 mg/dL, which recovered to normal levels by the end of the treatment period.

The incidence of hypocalcemia in the clinical trials for RGB-14 was low, which was expected given that the risk is highest in patients with renal impairment and/or inadequate calcium and vitamin D intake. Studies RGB-14-001 and RGB-14-101 both excluded patients with renal impairment (defined as eGFR < 30 mL/min)

Additionally, patients in both trials were also supplemented with calcium ≥ 1000mg daily and vitamin D ≥ 800 IU daily during the treatment period, which is consistent with the recommendations for calcium and vitamin D supplementation in product labeling.

Overall, the review team concluded that the risk of hypocalcemia associated with RGB-14-P was consistent with that of Prolia.

5 Expected Postmarket Use

Enoby is expected to be administered by healthcare providers in an outpatient setting. The patient and prescriber population for Enoby are expected to be similar to those of Prolia.[f] Primary care providers, endocrinologists, rheumatologists, and gynecologists are expected to comprise the majority of

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved*.

prescribers. Patient with severe renal impairment, including dialysis-dependent patients, are at highest risk of hypocalcemia while on Enoby. These patients are also expected to have a care team who is familiar with the risks of denosumab therapy as well as management of electrolyte imbalances in patients with kidney disease.

6 Review of the Proposed REMS

The proposed REMS submitted by Hikma on September 27, 2024, and amended on April 1, 2025 and June 20, 2025, includes the following REMS elements: a communication plan and timetable for submission of assessments.

6.1 REMS Goal(s)

Hikma proposed the following REMS goal for Enoby:

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

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 m2)
- Need to assess for presence of chronic kidney disease-mineral bone disorder (CKD-MBD) before initiating ENOBY in patients with advanced chronic kidney disease

Reviewer Comments: *The proposed goal and objective are acceptable. The REMS goal and objective for Enoby are the same as the currently approved goal for the Prolia REMS.*

6.2 REMS Document

Hikma submitted a REMS Document that is comparable to the most recently approved Prolia REMS, and the format and content is consistent with the recommendations in the Format and Content of a REMS Document Guidance for Industry and the REMS Document Technical Conformance Guide.

Reviewer Comments: *The Enoby REMS Document is acceptable.*

6.3 REMS Requirements

The proposed elements of the Enoby REMS are the same as the currently approved Prolia REMS, and includes a communication plan and timetable for submission of assessments. The communication plan consists of the following materials:

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

Reviewer Comments: *The REMS requirements and associated communication plan materials are comparable to those of the Prolia REMS, are expected to provide an equivalent level of safety to the approved Prolia REMS, and are therefore acceptable.*

7 Timetable for Submission of Assessments

Hikma is required to submit REMS assessments at 18 months, 3 years, and 7 years from the date of the initial REMS approval.

Reviewer Comments: *This submission timetable mirrors that of the Prolia REMS. The timetable for submission of assessments is acceptable.*

8 Supporting Document

The Enoby REMS Supporting Document contains the REMS program background information and a description of the operations of the REMS. This includes the details of the dissemination of the communication plan (CP) materials, as well as the processes that will be followed when items are undeliverable. Hikma detailed how the REMS will be operated, monitored, and assessed to ensure compliance with the REMS requirements. The Assessment Plan within the REMS Supporting Document includes metrics to inform program evaluation. The REMS Supporting Document also includes a description of the Key Performance Indicator and its target threshold, and Key Risk Messages which identify critical safety information.

Reviewer Comments: *The applicant appropriately addressed all comments made by DRM and DMAMES related to the REMS Supporting Document. The REMS Supporting Document submitted on August 12, 2025 is 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. The KRMs are based on the REMS goals and objectives and guide the messaging throughout the REMS materials. The proposed KRMs are as follows:

Healthcare Providers:

- There is a risk of severe hypocalcemia in patients with advanced chronic kidney disease (eGFR < 30 mL/mind/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 Enoby.
- Coordinate care with health care providers with expertise in CKD-MBD for patients with advanced chronic kidney disease during treatment with Enoby.

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 Comments**: The proposed KRMs are acceptable.*

8.2 Key Performance Indicators (KPIs)

This section includes the KPIs, KPI thresholds and supporting rationale, and what actions may be taken in the KPI thresholds are not met. The proposed KPIs for the Enoby 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 ENOBY	% of healthcare providers knowledgeable on the risk of severe hypocalcemia in patients with advanced CKD and need to assess for presence of CKD-MBD before initiating ENOBY	≥ 80% targeted knowledge threshold

***Reviewer Comment**: The KPI is 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 Program 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 will aid in determining if the REMS is operating as intended and meeting its goal and objective.

***Reviewer's Comments**: DMAMES reviewed the initial September 27, 2024, submission of the Assessment Plan and provided the Applicant with a minor editorial comment in the August 05, 2025, Agency*

comments. The Applicant accepted and incorporated the requested revision in their August 12, 2025, REMS amendment. The Assessment Plan included in the REMS Supporting Document of the August 12, 2025, submission is acceptable and is included in the Appendix of this review.

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

9.1 Impact on Burden for Healthcare Providers

The currently approved Prolia REMS consists of a Communication Plan, ***without*** Elements to Assure Safe Use (ETASU) linked to prescribing or dispensing, and thus does not add significant burden to the process of prescribing the drug. The Enoby REMS is structured similarly and should add minimal burden for providers. There is potential for perceived burden resulting from confusion for healthcare providers due to receiving multiple letters from the various approved denosumab REMS. The Enoby REMS materials will be comparable to the Prolia REMS materials, to minimize conflicting messaging. For providers already familiar with the risks of Prolia and other denosumab products, the Enoby REMS materials will communicate the same key risk messages as the Prolia REMS.

9.2 Impact on Access and Burden for Patients

The Enoby REMS does not require patient enrollment and burden for patients is expected to be minimal.

9.3 Impact on Safe Use of Denosumab

The Enoby REMS is expected to provide the same level of safety as the approved Prolia REMS, while adding minimal burden for stakeholders. The availability of an additional denosumab biosimilar product is expected to provide additional options for prescribers and patients. The dissemination of the Enoby REMS materials may also inform a greater number of prescribers about the risks associated with denosumab products.

10 Discussion

The review team recommends approval of Enoby based on the efficacy and safety information provided in the application.

The serious risk associated with the RLD, Prolia, is the risk of severe hypocalcemia in patients with advanced chronic kidney disease (CKD), including dialysis-dependent patients. Prolia is subject to a REMS to mitigate this risk. A REMS is necessary to ensure the benefits of Enoby outweigh the risk of severe hypocalcemia in patients with advanced chronic kidney disease (CKD), including dialysis-dependent patients. The Applicant submitted the Enoby REMS proposal on September 27, 2024, and it was last amended on August 12, 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 biosimilar REMS has the potential to introduce some burden on the healthcare system. However, the burden is expected to be minimal as

the requirements and risk messaging are the same across all denosumab REMS programs, and the programs do not require providers or patients to enroll. 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 Enoby will achieve the same level of patient safety as the approved Prolia REMS that was last modified on April 9, 2024.

11 Conclusion & Recommendations

DRM finds the proposed Enoby REMS to be acceptable and recommends approval of the REMS as submitted on August 12, 2025.

12 Appendices

12.1 Assessment Plan

The REMS assessment plan must include, but is not limited to, the following items:

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.
        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 for 18-month report only):**
    a. *Date of first commercial availability of Enoby
    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. Enoby utilization information including but not limited to indication and type of HCP (i.e., endocrinologist, general practitioner, internist, etc.)

Knowledge

4. **Evaluation of HCP's 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 Enoby; 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 Enoby, 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.

12.2 REMS MATERIALS

Training and Educational Materials

1) Patient Guide

Communication Materials

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

Other Materials

4) REMS Website

13 References

[1] Crisostomo, N. DGE. Approval of denosumab, BLA 125320. June 1, 2010.

[2] Hanan, E. DGE. Approval of Prolia REMS modification, BLA 125320. April 9, 2024.

[3] Cabellon, N. DGE. Approval of denosumab biosimilar, BLA 761362. March 5, 2024.

[4] Johnson, J. DGE. Approval of denosumab biosimilar, BLA 761392. February 13, 2025.

[5] Cabellon, N. DGE. Approval of denosumab biosimilar, BLA 761404. February 28, 2025.

[6] Van Der Waag, J. DGE. Approval of denosumab biosimilar, BLA 761398. March 25, 2025.

[7] Lee, A. DGE. Approval of denosumab biosimilar, BLA 761444. August 29, 2025.

[8] Jairath, M. DGE. Approval of denosumab biosimilar, BLA 761436. September 16, 2025.

[9] Hanan, E. DGE. Approval of Prolia REMS modification, BLA 125320. March 5, 2024.

[10] Hikma. BLA 761439 (Enoby) submission, September 27, 2024.

[11] Hou, S. DGE. Information request for BLA 761439, March 22, 2025.

[12] Hikma. Amendment to BLA 761439 (sequence #0019), April 17, 2025.

[13] Hou, S. DGE. Information request for BLA 761439, August 5, 2025.

[14] Hikma. Amendment to BLA 761439 (sequence #0032), August 12, 2025.

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/s/

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