CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761398Orig1s000
761398Orig2s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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: 761398
Products: Conexxence (denosumab- bnht), injectrion
APPLICANT: Fresenius Kabi USA, LLC
FROM: Marina Zemskova, M.D., Deputy Director for Safety
DATE: 3/20/2025

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 Conexxence 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. Conexxence 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. Conexxence has the same mechanism(s) of action, route of administration, dosage form, strengths, and conditions of use as those of Prolia. Since Conexxence shares the same mechanism of action (i.e., functions as a RANKL inhibitor), efficacy across indications is extrapolated for Conexxence. 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. Conexxence 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. Conexxenceis 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)
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	761398
PDUFA Goal Date	March 25, 2025
Nexus TTT #	2024-8849, 2024-8852
Reviewer Name	Courtney Cunningham, PharmD
Team Leader	Yasmeen Abou-Sayed, PharmD
Review Completion Date	March 20, 2025
Subject	Evaluation of Need for a REMS
Established Name	Denosumab-bnht
Trade Name	Conexxence
Name of Applicant	Fresenius Kabi USA, Inc.
Therapeutic Class	Rank Ligand (RANKL) Inhibitor
Dosage Formulation	60 mg/mL solution in a single-dose prefilled syringe
Dosing Regimen	60 mg every 6 months as a subcutaneous (SC) 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 Conexxence (denosumab-bnht), Biologic Licensing Application (BLA) 761398, submitted by Fresenius Kabi USA, Inc. (Fresenius Kabi) on March 27, 2024, and amended on June 14, 2024, October 8, 2024, February 18, 2025, and February 21, 2025. Fresenius Kabi USA, Inc. proposes denosumab-bnht as an interchangeable biosimilar to the United States (US) licensed Prolia and Xgeva (denosumab), BLA 125320, under the proprietary names Conexxence and Bromyntra, respectively. The proposed presentations and routes of administration for Conexxence are the same as the reference listed drug (RLD). The application is under review in both the Division of General Endocrinology (DGE) and the Office of Therapeutic Biologics and Biosimilars (OTBB). Fresenius Kabi is seeking approval for the following same indications as the RLD:

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

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 Conexxence REMS proposed by Fresenius Kabi are the same as those for the currently approved Prolia REMS and include a CP and timetable for submission of assessments. The requirements of the Conexxence REMS will apply to any unbranded denosumab-bnht products distributed by the Applicant.

DRM has determined that the proposed REMS for Conexxence is acceptable and communicates the same key risk messages as the Prolia REMS to achieve equivalent safety. DMAMES also found the REMS Assessment Plan as submitted on February 21, 2025, to be acceptable.[1]

The Conexxence REMS, as submitted on February 21, 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 Conexxence (denosumab-bnht) biologic licenses application (BLA) 761398, submitted by Fresenius Kabi US, Inc. (Fresenius Kabi) on March 27, 2024, and amended on June 14, 2024, October 8, 2024, February 18, 2025, and February 21, 2025, to determine if the REMS achieves the equivalent safety as the REMS for Prolia, the reference listed drug (RLD). The application is under review both the Division of General Endocrinology (DGE) and the Office of Therapeutic Biologics and Biosimilars (OTBB).

Fresenius Kabi has proposed the following same indications,[a] for Conexxence as Prolia, and the RLD:

- Treatment of postmenopausal women with osteoporosis at high risk of fracture
- Treatment to increase bone mass in men with osteoporosis at high risk for fracture
- Treatment of glucocorticoid-induced osteoporosis in men and women with high risk of fracture
- Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer

The applicant's proposed REMS consists of a communication plan (CP) and a timetable for submission of assessments, which are the same components as the Prolia REMS.

2. Background

2.1. Product Information

Denosumab is a human monoclonal IgG2 antibody targeting the nuclear factor kappa B ligand (RANKL) receptor activator. The recommended dose of Conexxence is 60 mg subcutaneously every 6 months, administered in a clinical setting by a healthcare provider.[b] Fresenius Kabi has developed denosumab-bnht with proposed proprietary names Conexxence and Bromyntra as interchangeable biosimilars to US-Prolia and US-Xgeva, respectively. Prolia (BLA 125320), the RLD for Conexxence, has been approved in the US since 2010, and is available as a 60 mg/mL subcutaneous injection in a prefilled syringe. In the US, Prolia is approved with a REMS to mitigate the risk of severe hypocalcemia in patients with advanced chronic kidney disease, including those patients who are dialysis dependent.

Denosumab is also approved in the US as Xgeva (90 mg/mL and 120 mg/1.7 mL in single dose vials) for other indications. Multiple biosimilars have been approved and are outlined in the table below.[c]

Table 1. Approved Denosumab Biosimilars

Proper Name	Trade Name	Date Approved	Application Number
Denosumab-bbdz	Jubbonti (60 mg/mL) PFS Wyost (70 mg/mL and 120 mg/1.7 mL) single dose vial	March 5, 2024[2]	BLA 761362
Denosumab-dssb	Ospomyv (60 mg/mL) PFS Xbryk (70 mg/mL and 120 mg/1.7 mL) single dose vial	February 13, 2025[3]	BLA761392

[a] 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.*

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

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

Denosumab-bmwo	Stoboclo (60 mg/mL) PFS Osenvelt (70 mg/mL and 120 mg/1.7 mL) single dose vial	February 28, 2025[4]	BLA 761404

2.2. Prolia REMS

To ensure its benefits outweighed its risks of osteonecrosis of the jaw, serious infections, and dermatologic reactions, Prolia was required at approval (June 1, 2010) to have a REMS. In 2012, additional risks of atypical femur fracture and hypocalcemia were included in the REMS. The REMS has been modified 14 times and was last modified on April 9, 2024 to remove four of the five risks and focus on the risk of severe hypocalcemia. The current Prolia REMS is as follows:

Table 2: Summary of Approved Prolia REMS

REMS GOAL	To mitigate the risk of severe hypocalcemia in patients with advanced chronic kidney disease (CKD), including dialysis-depending patients, associated with Prolia.
	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 Prolia in patients with advanced chronic kidney disease
Elements of the REMS	Communication Plan • Patient Guide • REMS Letter for Healthcare Providers • REMS Letter for Professional Societies • REMS Website
Timetable for Submission of Assessments	18-months, 3-years, and 7-years from date of REMS modification approval of March 5, 2024

2.3. Regulatory History

The following is a summary of the regulatory history for BLA 761398 relevant to this review:

- 03/27/24: Applicant submitted BLA 761398 for FKS518 (denosumab-xxxx) as a biosimilar to both Prolia and Xgeva.

- 05/21/24: DRM sent comments and redlined materials to the Applicant requesting a complete submission that included a REMS Supporting Document.
- 06/14/24: Fresenius Kabi USA, Inc., submitted an amendment to the REMS.
- 09/12/24: DRM and the Division of Mitigation Assessment and Medication Error Surveillance (DMAMES) sent interim comments on the 6/14/24 REMS submission.
- 10/08/24: Fresenius Kabi submitted a REMS amendment in response to the 9/12/24 comments.
- 12/18/24: In a Late Cycle Meeting, the Applicant asked the Agency to confirm that the proposed REMS could be utilized for not only the branded biosimilar, but also for the unbranded biosimilar. DRM answered that the proposed REMS, with some edits, will suffice for both products and that a redlined REMS document would be provided in upcoming comments on the submission.[5]
- 01/31/2025: DRM and DMAMES sent interim comments on the 10/08/24 REMS submission.
- 02/18/25: Fresenius Kabi submitted an amendment to the REMS in response to the 1/31/25 comments.
- 02/19/25: DRM sent a correspondence to Fresenius Kabi asking for a complete submission as the 02/18/25 submission was incomplete.
- 02/21/25: Fresenius Kabi sent a REMS amendment in response to the 02/29/25 correspondence.

3. Benefit Assessment

The biosimilarity of denosumab-bnht to US-Prolia was evaluated in FKS518-001, a Phase 1 pharmacokinetic study similarity study and a Phase 3 comparative clinical study.

FKS518-001 was a double-blind, randomized, 2-arm, single-dose, parallel group phase 1 study in 214 healthy male subjects to compare the pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of denosumab-bnht and US-Prolia. The primary PK endpoints were area under the concentration time curve (AUC) from time zero to infinity ($AUC_{0\text{-inf}}$), last quantifiable concentration ($AUC_{0\text{-last}}$), and maximum observed serum concentration (C_{max}). The study, which 96.3% of subjects completed, demonstrated no clinically meaningful difference in denosumab-bnht and US-Prolia, with all parameters meeting the similarity criteria of 90% confidence interval of geometric least squares mean ratio of denosumab-bnht/US-Prolia withing the limits of 80.00% - 125.00%.[6]

Table 3. Summary of Primary Pharmacokinetic Parameters

Outcome Measure (Measure Description)	Treatment Comparison and Similarity Criterion (95% Confidence Interval [CI] of the Geometric Least Squares Mean Ratios (GLSM) [80.00% - 125.00%]		
	Denosumab-bnht	US Prolia	Ratio (%)
$AUC_{0\text{-inf}}$ (h • µg/mL)	6411 (5911, 6952)	5691 (5232, 6189)	112.65 (104.27, 121.70)

$AUC_{0\text{-last}}$ (h ·µg/mL)	6268 (5792, 6783)	5582 (5145, 6056)	112.29 (104.17, 121.04)
C_{max} (µg/mL)	5.36 (4.94, 5.81)	5.11 (4.70, 5.56)	104.79 (97.04, 113.15)

Source: Section 5.3.1 Study FKS518-001, Figure 3, BMER; Table 9, Study FKS518-001 CSR

The applicant collected and analyzed PD data in study FKS518-002, which were evaluated only to ensure the findings did not conflict with the other data, which it did not.

FKS518-002 was a double-blind, randomized, multicenter, multiple-dose, 2-arm, parallel group study in 553 post-menopausal women with osteoporosis to compare the pharmacodynamics, efficacy, safety, and immunogenicity of denosumab-bnht to US-Prolia. Subjects were randomized 1:1 to Prolia or denosumab-bnht, injected once every 6 months for 52 weeks (months 0 and 6) during this "Core Period", then at 52 weeks, subjects in the US-Prolia arm were rerandomized to either continue Prolia or transition to denosumab-bnht (month 12). Those who received denosumab-bnht during the first year remained on denosumab and were followed up to week 72 during this "Transition Period". The PK mean study drug concentration-time profiles are similar between denosumab-bnht and US-Prolia, and the PD statistical analysis also determined PD equivalence. Immunogenicity was assessed in both studies, and supports the lack of impact on the PK per the review.[6] The primary efficacy endpoint was the percentage change in lumbar spine bone mineral density (LS-BMD) assessed by DXA at week 52 compared to baseline. The difference in the mean percentage change from baseline in LS-BMD was 0.46 (90% CI [-0.05, 0.96]) when testing non-inferiority, and 0.69 (90% CI [0.19, 1.20]) when testing non-superiority.[d]

From the primary PK data from study FKS518-001 and additional data from study FKS518-002, the clinical review team concluded that biosimilarity was established between denosumab-bnht and US-Prolia.

4. Risk Assessment and Safe Use Conditions

The primary data for the safety review of denosumab-bnht relies on data from study FKS518-002, with data from FKS518-001 examined for known risk of denosumab.

There were no deaths in either study.

Twenty-three subjects experienced a serious adverse event (SAE) in study FKS518-001, with 14 in the denosumab-bnht group and 9 in the US-Prolia group. All but two were COVID-19 infections. One subject experienced a suicide attempt and another experienced biliary duct adenocarcinoma. Neither were determined to be related to study drug, and both occurred in the denosumab-bnht group. In study FKS518-002, during the Core Period, serious adverse events occurred in 43/277 (15.5%) of denosumab-

[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.*

bnht subjects and 50/276 (18.1%) US-Prolia taking subjects. COVID-19 and its symptoms were the most commonly reported adverse events. Of the remaining SAEs, there was a higher incidence of new malignancies in the US-Prolia group, which the clinical reviewer notes is likely due to chance. In the Transition Period, 8/252 (3.2%) of denosumab-bnht subjects experienced a During the Transition Period, 8/252 (3.2%) subjects in the denosumab-bnht to denosumab-bnht group, 6/124 (4.8%) subjects in the US-Prolia to denosumab-bnht group, and 6/125 (4.8%) subjects in the US-Prolia to US-Prolia group experienced treatment-emergent serious adverse events. As in the Core Period, the most frequently reported events were COVID-19 related.

The most common treatment emergent adverse events (TEAEs) outside of those related to the COVID-19 pandemic align with the known safety profile of denosumab, with no new safety signals being seen.

4.1. Hypocalcemia

Hypocalcemia, particularly in patients with a bone mineral disorder, is a known risk of denosumab.[e] The risk is highlighted in the US prescribing information for Prolia in a boxed warning. In study FKS518-001, there were no meaningful differences in chemistry panels between subjects treated with US-Prolia and denosumab-bnht, nor did any subjects serum calcium fall below 8.58 mg/dL, the lower limit of normal. Subjects in FKS519-002 were instructed to take 1,000mg of calcium and 400 IU vitamin D supplements daily. Subjects on dialysis or those with a creatinine clearance of <30mL/min were excluded from the study. The median change from baseline in serum calcium during the first 52 weeks of study FKS518-002 was comparable in both treatment groups, with it falling below 8 mg/dL once in two subjects only. The clinical reviewer also finds that in study weeks 52-78, there were no meaningful differences between the treatment groups in median changes in serum calcium. During the transition from US-Prolia to denosumab-bnht, there was a higher incidence in those who changed study products, but has been attributed to statistical chance.[6]

5. Expected Postmarket Use

Conexxence's prescribing and patient population are expected to be similar to those of Prolia, which include endocrinologists, gynecologists, rheumatologists, and primary care practitioners who care for patients with osteoporosis.[f] Patients with severe chronic kidney disease or are dialysis-dependent and are at highest risk of hypocalcemia with Conexxence therapy are also expected to have a care team of multiple providers expected to be familiar with risks associated with RANKL inhibitors. Conexxence is expected to be prescribed and administered in the outpatient clinical setting.

[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.*

[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.*

6. Review of the Proposed REMS

The proposed Conexxence REMS was submitted on March 27, 2024, and amended on June 14, 2024, October 8, 2024, February 18, 2025, and February 21, 2025.The Conexxence REMS includes a CP and timetable for submission of assessments.

6.1. REMS Goals

The proposed goal of the Conexxence REMS is the same as the currently approved goal for the Prolia REMS and is as follows: The goal of the Conexxence REMS is to mitigate the risk of severe hypocalcemia in patients with advanced chronic kidney disease (CKD), including dialysis-depending patients, associated with Conexxence.
Reviewer Comment: The proposed goal is acceptable.

6.2. REMS Requirements

The proposed elements of the Conexxence REMS are the same are the same as the currently approved Prolia REMS (see Section 2.2), as are the proposed REMS materials, which include a *REMS Letter for Healthcare Providers, REMS Letter for Professional Societies, REMS Patient Guide*, and a REMS website. As proposed, the Conexxence REMS will provide an equivalent level of safety for Conexxence as the Prolia REMS does for Prolia.

Reviewer Comment: We agree with the proposed Conexxence REMS. We find that the proposed REMS includes similar requirements to the approved Prolia REMS and is expected to provide an equivalent level of safety for Conexxence.

7. Timetable for Submission of Assessments

Fresenius Kabi is required to submit REMS assessments at 18 months, 3 years, and 7 years from the date of the initial REMS approval. This submission timetable mirrors that of the Prolia REMS.

Reviewer Comment: We find the proposed timetable for submission of REMS assessments acceptable.

8. Supporting Document

The Conexxence REMS Supporting Document contains operational and background information of the Conexxence REMS. This includes details of the plan for dissemination of the communication plan educational materials as well as contingencies for undeliverable forms of dissemination. Fresenius Kabi detailed how the REMS will operate, be monitored, and be assessed to ensure compliance with the REMS. The Assessment Plan is included in the REMS Supporting Document as well as metrics, such as Key Performance Indicators and Key Risk Messages which aid in determining if the REMS is meeting its goal and objectives.

Reviewer Comment: The Applicant submitted and appropriately addressed all comments made by DRM and DMAMES, and the REMS Supporting Document is acceptable as submitted on February 21, 2025.

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8.1. Key Risk Messages (KRMs)

The KRMs identify the 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, this is associated with Conexxence. 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/min/1.73 m2), including dialysis-dependent patients
- There is a need to assess patients for presence of chronic kidney disease-mineral bone disorder (CKD-MBD) before initiating Conexxence
- Coordinate care with health care providers with expertise in CKD-MBD for patients with advanced chronic kidney disease during treatment with Conexxence

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 Indicators (KPI)

This section includes the KPI, KPI thresholds, and supporting rationale, as well as what actions may be taken if the KPI thresholds are not met. The proposed KPIs for the Conexxence 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 Conexxence	% 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 Conexxence	≥ 80% targeted knowledge threshold

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.

Reviewer Comment: *The KPI for the Conexxence REMS is acceptable.*

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, Health Outcomes and/or Surrogates of Health Outcomes, Knowledge, 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 Comment: *The Applicant appropriately addressed our comments and the Assessment Plan submitted on October 4, 2024, is acceptable as determined in the August 30, 2024, review by DMAMES.*[1] *The Assessment Plan is included in the Appendix of this review and will be included in the action letter.*

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

9.1. Impact on Burden on 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 REMS. To reduce potential stakeholder burden for healthcare providers that may already be familiar with the risks associated with denosumab products, the Conexxence REMS materials will communicate the same key risk messages as the Prolia REMS.

9.2. Impact on Access and Burden on 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

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

10. Discussion

The Clinical Reviewer recommends approval of Conexxence on the basis of the efficacy and safety information currently available from the application. The serious risk associated with Prolia (RLD) is severe hypocalcemia in patients with advanced chronic kidney disease, including dialysis-dependent

Reference ID: 5553449

patients. Prolia is subject to a REMS to mitigate this risk. A REMS is necessary for Conexxence to ensure the benefits outweigh the risk of severe hypocalcemia in patients with advanced chronic kidney disease, including dialysis-dependent patients. The applicant submitted the Conexxence REMS proposal on March 27, 2024, and it was last amended on February 21, 2025. The proposed separate REMS consists of a communication plan (CP) and timetable for submission of assessments. The elements of the proposed REMS are the same as the currently approved REMS for the RLD.

We acknowledge that approving multiple denosumab biosimilar REMS will introduce some burden on the healthcare system, however, the burden is expected to be manageable as the requirements and risk messaging 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 the safety and burden of these REMS programs and determine whether any modifications are needed in the future.

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

11. Conclusions and Recommendations

DRM finds the proposed Conexxence REMS acceptable and recommends approval of the REMS as submitted on February 21, 2025. DMAMES reviewed the Conexxence REMS Assessment Plan and finds it acceptable as submitted on February 21, 2025.

Should DGE or OTBB have any concerns or questions or if new safety information becomes available, please send a consult to DRM.

12. Appendices

Conexxence REMS Assessment Plan

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

1. ***Program Outreach and Communication***

(a) REMS Communication Plan Activities (*provide data for 18-month report only)

i. *Number of healthcare providers (stratified by specialty) targeted by the REMS

ii. *Number of professional societies targeted, and which professional societies reported distribution of the REMS letter to their respective members

iii. *REMS Letters: A summary that includes the following information, stratified by distribution waves (i.e., date distributed):

Reference ID: 5553449

(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 Societies* 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.

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

v. Dates and names of the key Professional Meetings attended and corresponding information on the REMS materials displayed and/or distributed

2. Program Implementation and Operations

(a) Program Implementation (*Provide data for 18-month report only)

i. *Date of first commercial availability of Conexxence

ii. *Date when the REMS website went live

iii. Number of total visits and unique visits to the REMS website

iv. Number and type of REMS materials downloaded or accessed

(b) Utilization Data

i. Conexxence utilization information including but not limited to indication and type of healthcare provider (e.g., endocrinologists, rheumatologists, obstetricians/gynecologists, primary care physicians, oncologists, urologists)

3. Knowledge

(a) Evaluation of healthcare providers' knowledge:

i. An evaluation of healthcare providers' understanding of the risk of severe hypocalcemia in patients with advanced chronic kidney disease via analysis of assessment survey results, stratified by healthcare professional specialty (e.g., endocrinologists, rheumatologists, obstetricians/gynecologists, primary care physicians, oncologists, urologists)

ii. An evaluation of healthcare providers' understanding of the need to assess for presence of CKD-MBD before initiating Conexxence, stratified by healthcare provider specialty

iii. An evaluation of healthcare providers' understanding of the requirement to give each patient a copy of the *Patient Guide* via analysis of assessment survey results

4. ***Health Outcomes and/or Surrogates of Health Outcomes***

(a) Safety Surveillance:

i. A summary and analysis of all post-marketing case reports of severe hypocalcemia associated with Conexxence, stratified by kidney function

5. ***Overall Assessment of REMS Effectiveness***

Reference ID: 5553449

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.

13. References

1. Elame, Y., Final BLA 761398 REMS Assessment Plan Review Interim Comments, August 30, 2024, DARRTS ID # 14249937.
2. Cabellon, N. DGE. Approval of denosumab biosimilar, BLA 761362, March 5, 2024.
3. Johnson, J. Approval of denosumab biosimilar, BLA 761392, February 13, 2025.
4. Cabellon, N. DGE. Approval of denosumab biosimilar, BLA 761404. February 28, 2025.
5. Van der Waag, J., Minutes from the December 18, 2024 Late Cycle Meeting for Denosumab-bnht (BLA 761398), January 16, 2025, DARRTS ID 5512683.
6. DGE, OTBB., Draft BMER for Denosumab-bnht (BLA 761398), March 12, 2025.

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Reference ID: 5553449

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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	761398
Supplement Number, Date Received	Received October 8, 2024 (sequence 18)
Action Date	March 25, 2025
Nexus TTT #	2024-8849, 2024-8852
Reviewer Name	Courtney Cunningham PharmD
Team Leader	Yasmeen Abou-Sayed, PharmD
Review Completion Date	January 31, 2025
Subject	Review of proposed REMS
Established Name	Denosumab-bnht
Trade Name	Conexxence
Name of Applicant	Fresenius Kabi USA, Inc.
Therapeutic Class	Rank L inhibitor
Formulation	60mg/mL solution in a single-dose prefilled syringe

Reference ID: 5521908

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Reference ID: 5521908

1 Introduction

These comments by the Division of Risk Management (DRM) pertain to the proposed REMS for Conexxence (denosumab-bnht) and denosumab-bnht (unbranded biosimilar), Biologic Licensing Application (BLA) 761398, submitted by Fresenius Kabi, USA, Inc., on March 27, 2024, and amended on June 14, 2024, and October 8, 2024. Fresenius Kabi, USA, Inc., proposes denosumab-bnht as an interchangeable biosimilar to the United States licensed Prolia and Xgeva (denosumab), BLA 125320 under the proposed proprietary names Conexxence and Bomyntra. The proposed indications and routes of administration are the same as the US-licensed products with the exception being the addition of a proposed 120mg prefilled syringe for the Bomyntra product. The proposed indications for Conexxence are for the treatment of those who are high risk of fracture: (1) postmenopausal women with osteoporosis, (2) increase bone mass in men, (3) glucocorticoid-induced osteoporosis in men and women, (4) increase bone mass in men receiving androgen deprivation therapy for nonmetastatic prostate cancer, and (5) increase bone mass in women 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 risk messaging in the proposed Conexxence REMS will align with the Prolia REMS and will include a communication plan and timetable for submission of assessments.

1.1 REGULATORY HISTORY

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

- 03/27/24: Submission of FKS518 (denosumab-xxxx) as a biosimilar to both Prolia and Xgeva received.
- 05/21/24: DRM sent comments and redlined materials to the Applicant requesting a complete submission that included a REMS Supporting Document.
- 06/14/24: Fresenius Kabi USA, Inc., submitted an amendment to the REMS
- 09/12/24: DRM and the Division of Mitigation Assessment and Medication Error Surveillance (DMAMES) sent interim comments on the 6/14/24 REMS submission.
- 10/08/24: Fresenius Kabi submitted a REMS amendment in response to the 10/08/24 comments.
- 12/18/2024: In a Late Cycle Meeting, the Applicant asked the Agency to confirm that the proposed REMS could be utilized for not only the branded biosimilar, but also for the unbranded biosimilar. DRM answered that the proposed REMS, with some edits, will suffice for both products and that a redlined REMS document would be provided in upcoming comments on the submission.

2 Comments to the Applicant

We have the following comments on the proposed Conexxence and unbranded biologic REMS, submitted on October 8, 2024:

<u>Throughout the REMS:</u>

- Update the product's suffix in the REMS document and throughout all REMS materials

Reference ID: 5521908

REMS Document:

- See attached redlined REMS document for additions to include the unbranded biosimilar and minor formatting edits.

REMS Website:

- Add the details “including dialysis-dependent patients, following Conexxence administration” to the bullet point “severe hypocalcemia in patients with advanced chronic kidney disease.” See redlined document.

Supporting Document:

- Move the Key Risk Messages and Key Performance Indicator sections directly ahead of the Assessment Plan portion of the Supporting Document.
- See redlined edits for clarity and consistency throughout the Supporting Document.

Please submit a REMS amendment including redlined and clean Word versions, as well as clean pdf versions of the REMS document and all appended materials, as well as the REMS Supporting Document by close of business February 17, 2025.

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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	761398
PDUFA Goal Date	March 25, 2025
Nexus TTT #	2024-8849, 2024-8852
Reviewer Names	Courtney Cunningham, PharmD
Team Leaders	Yasmeen Abou-Sayed, PharmD
Review Completion Date	September 12, 2024
Subject	Comments to the Applicant regarding the Proposed REMS
Established Name	FKS518 (denosumab)
Proposed Trade Name	Conexxence
Name of Applicant	Fresenius Kabi USA, Inc.
Therapeutic Class	Rank L inhibitor
Formulation	60 mg/1mL solution in a single-dose prefilled syringe
Dosing Regimen	60 mg every 6 months as a subcutaneous injection

Reference ID: 5445268

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Reference ID: 5445268

1 Introduction

These comments by the Division of Risk Management (DRM) and the Division of Mitigation Assessment and Medication Error Surveillance (DMAMES) pertain to the proposed REMS for Conexxence (FKS518, denosumab), Biologic Licensing Application (BLA) 761398, submitted by Fresenius Kabi, USA, Inc., on March 27, 2024, and amended on June 14, 2024. Fresenius Kabi, USA, Inc., proposes FKS518 as an interchangeable biosimilar to the United States licensed Prolia and Xgeva (denosumab), BLA 125320 under the proposed proprietary names Conexxence and Bomyntra. The proposed indications and routes of administration are the same as the US-licensed products with the exception being the addition of a proposed 120mg prefilled syringe for the Bomyntra product. The proposed indications for Conexxence are for the treatment of those who are high risk of fracture: (1) postmenopausal women with osteoporosis, (2) increase bone mass in men, (3) glucocorticoid-induced osteoporosis in men and women, (4) increase bone mass in men receiving androgen deprivation therapy for nonmetastatic prostate cancer, and (5) increase bone mass in women 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 risk messaging in the proposed Conexxence REMS will align with the Prolia REMS and will include a communication plan and timetable for submission of assessments.

1.1 REGULATORY HISTORY

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

- 03/27/24: Submission of FKS518 as a biosimilar to both Prolia and Xgeva received with incomplete REMS for the Prolia biosimilar
- 05/21/24: DRM sent comments and redlined materials to the Applicant based on the initial submission, as well as requesting a complete submission that included a REMS Supporting Document with the next amendment
- 06/14/2024: Fresenius Kabi USA, Inc., submitted a complete REMS correspondence to the Agency

2 Comments to the Applicant

We have the following comments on the proposed Denosumab-xxxx REMS, submitted on June 14, 2024:

REMS Document:

- In Section 2, under Object 1, the 2 in m^2 should be in superscript
- In Section 3, the introductory paragraph beginning “To inform healthcare providers” should not be in bold type
- In the table under Section 3, in point #3 in the REMS Letters portion, “REMS Website” should be in blue as a REMS material

Letter for Healthcare Professionals:

- Ensure Drug name/logo is also on the material, not just Fresenius Kabi Logo (in this case, on the top left corner)

Reference ID: 5445268

Letter for Professional Societies:

- Ensure Drug name/logo is also on the material, not just Fresenius Kabi Logo (in this case, on the top left corner)
- Heading in red just below "Month YYYY" should read "Important Safety Update" not (b) (4)

Patient Guide

- Ensure Drug name/logo is also on the material, not just Fresenius Kabi Logo
- The last line of the guide that begins "if you have chronic kidney disease…" should be bolded to call attention to the information in the pdf version as it is in the Word versions of the REMS materials.

Website Screenshots:

- Link to Guide link may remain or may be removed as it is not an element of the REMS
- Add the screenshot of the landing page for the "Contact Us" link on the homepage. Consider information such as, "If you have questions about the 'Proprietary Name' REMS, a clinical inquiry, or want to report an adverse event relates to 'Proprietary Name' call 1-800-XXX-XXXX" to enable stakeholders to easily find information, as well as a clickable link for questions or adverse event reports.

Supporting Document:

- Section A of the Supporting Document (information about Fresenius Kabi) may be deleted
- Section IV entitled "Supporting information on proposed REMS elements" should be retitled "REMS Elements"

Assessment Plan:

The Agency requires revisions to the REMS Assessment Plan. The changes are summarized below, and a tracked changed version is attached with additions underlined and deletions in ~~strikethrough~~.

- Metric number 3b: *Report on Key Performance Indicator (KPI)* was deleted. Information on the KPI should be relocated to a different section of the REMS Supporting Document, outside the Assessment Plan metrics. Create a new section of the REMS Supporting Document that defines the KPI, the metrics to inform the KPI, the target threshold for the KPI, and the rationale for the target threshold. Refer to the Agency Information Request dated May 21, 2024, for more information on where to place the information on the KPI within the REMS Supporting Document.

Please submit a REMS amendment including redlined and clean Word versions, as well as clean pdf versions of the REMS document and all appended materials, as well as the REMS Supporting Document by close of business October 8, 2024.

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REMS Assessment Plan Review

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)

*****This document may contain information that cannot be released to the public*****

Application Type	BLA
Application Number	761398
Task Tracking Tool Number	2024-9893
Submission Type/Number	Original-1/8
Submission Date	June 14, 2024
Reviewer	Yanick Elame, PharmD
Team Lead	Page Crew, PharmD, MPH, BCPS
Deputy Director	CDR Zachary Oleszczuk, PharmD, MSPharm, BCGP
Review Completion Date	August 30, 2024
Established Name	Denosumab
Product Code Name	FKS518[a]
Subject	Interim Comments for the FKS518 Risk Evaluation and Mitigation Strategies (REMS) Assessment Plan
Applicant	Fresenius Kabi USA, LLC
Therapeutic Class	RANK ligand (RANKL) inhibitor
Dosage Form and Strength	Injection 60 mg/mL

[a] At the time of initial submission on March 25, 2024, the proprietary name was not yet granted. On June 18, 2024, a Propriety Name Granted communication was issued to the Applicant, informing them that their proposed proprietary name, Conexxence, was conditionally acceptable. The June 18, 2024 communication is available from: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af8074efa2

1. Introduction

This review is in reference to the proposed Risk Evaluation and Mitigation Strategy (REMS) Assessment Plan for the proposed FKS518 REMS.

FKS518 is a RANK ligand (RANKL) inhibitor, proposed as an interchangeable biosimilar to the reference products, US-licensed Prolia and US-licensed Xgeva (both licensed under BLA 125320 by Amgen Inc.). The reference product Prolia has an approved REMS that includes a Communication Plan, and a Timetable for Submission of Assessments.

The proposed indications for FKS518 are the same as those for Prolia and include:

- 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 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

2. Background

On March 25, 2024,[b] the Applicant submitted an original Biologics License Application (BLA 761398) that included a REMS that is comparable to the reference product Prolia. The Proposed REMS submission however did not include a REMS Supporting Document (RSD).

On June 14, 2024,[c] in response to a May 21, 2024, Agency Information Request (IR), the Applicant resubmitted a REMS amendment, that included a REMS Supporting Document (RSD). Contained within the RSD is the proposed Assessment Plan for the FKS518 REMS

2.1 REMS Goal, Elements, and Timetable for Submission of Assessments

Goal

The goal of the proposed FKS518 REMS is to mitigate the risk of severe hypocalcemia in patients with advanced chronic kidney disease (CKD), including dialysis-dependent patients associated with FKS518.

Objective 1: Inform healthcare providers on:

- Risk of severe hypocalcemia 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 FKS518 in patients with advanced chronic kidney disease

Elements

The proposed FKS518 REMS consists of a Communication Plan only.

[b] The March 25, 2024 Original BLA Application is available at: \\CDSESUB1\EVSPROD\bla761398\0001\

[c] The June 14, 2024 REMS amendment/IR response is available from: \\CDSESUB1\EVSPROD\bla761398\0007\m1\us\116-risk-management\

Timetable for Submission of Assessments:
The proposed timetable for submission of assessments is at 18 months, 3 years, and 7 years from the date of the initial REMS approval. This proposed timetable for submission of assessments is the same as that of the reference product Prolia.

3. Review of the REMS Assessment Plan

The Applicant's proposed FKS518 REMS Assessment Plan is contained within the submitted REMS Supporting Document, which can be accessed from:

\\CDSESUB1\EVSPROD\bla761398\0007\m1\us\116-risk-management\1162-rems\rems-supporting-document.pdf

The Applicant intends to disseminate REMS communication materials (REMS letters, and a Patient Guide) to different stakeholders according to a prespecified timetable. The proposed Assessment Plan includes several metrics grouped under the following four headings:

1. *Program Outreach and Communication:*
   This section contains metrics that track the launch of the Communication Plan, and the number/type of letters sent to the different stakeholders. It also contains metrics assessing distribution of the REMS letters, and the presentation of FKS518 REMS materials at key professional meetings.

2. *Program Implementation and Operations:*
   This section contains metrics that track the implementation and operationalization of the REMS such as the date of commercial availability and launch of the website. The section also includes FKS518 utilization data, stratified by indication and healthcare provider (HCP) specialty.

3. *Knowledge:*
   This section proposes to evaluate HCP's understanding of the risk of severe hypocalcemia in patients with advanced chronic kidney disease, and the need to assess for the presence of CKD-MBD before initiating therapy, as well as HCP understanding of the requirement to give each patient a copy of the Patient Guide.

   In addition, this section includes metrics on the knowledge threshold (Key Performance Indicator [KPI]) that the Applicant proposed to be used to evaluate the FKS518 REMS

4. *Health Outcomes and/or Surrogates of Health Outcomes*
   This section includes a summary and analysis of all post-marketing case reports of severe hypocalcemia associated with FKS518.

Overall, the proposed Assessment Plan aligns with other REMS that are designed to mitigate similar risks. As mentioned above, on May 21 2024,[d] the Agency sent an IR to the Applicant instructing the Applicant to include a KPI for the FKS518 REMS in the REMS Supporting Document (prior to the Assessment Plan). The proposed KPI was provided to the Applicant by the Agency. However, in the current submission, the Applicant incorporated the KPI information for the FKS518 REMS into the knowledge metrics of the Assessment Plan (instead of before the Assessment Plan as requested by the

[d] The May 21, 2021 Information Request to the Applicant is available at:
https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af807466da

Agency in the May 21, 2024, IR). The Applicant will be asked to revise the Assessment Plan and REMS Supporting Document accordingly. See comments to the Applicant in section 5.

4. Conclusions and Recommendations

The REMS Assessment Plan contained within the Supporting Document of the June 14, 2024 FKS518 REMS amendment submission must be revised to relocate information on the Key Performance Indicator from the Assessment Plan metrics to the REMS Supporting Document. We recommend sending the comments in Section 5 and the revised Assessment Plan to the Applicant.

5. Comments to the Applicant

We have the following comments regarding the proposed FKS518 REMS Assessment Plan, submitted on June 14, 2024. Review of the REMS proposal is ongoing, and these comments should not be considered final.

REMS Assessment Plan

The Agency requires revisions to the REMS Assessment Plan. The changes are summarized below, and a tracked changed version is attached with additions underlined and deletions in ~~strikethrough~~.

- Metric number 3b: *Report on Key Performance Indicator (KPI)* was deleted. Information on the KPI should be relocated to a different section of the REMS Supporting Document, outside the Assessment Plan metrics. Create a new section of the REMS Supporting Document that defines the KPI, the metrics to inform the KPI, the target threshold for the KPI, and the rationale for the target threshold. Refer to the Agency Information Request dated May 21, 2024, for more information on where to place the information on the KPI within the REMS Supporting Document.

Resubmission Instructions

Within 10 business days of receipt of this communication, submit a REMS amendment that addresses these comments. Include in your response an updated REMS Supporting Document including the revised REMS Assessment Plan in Word tracked changes, Word clean, and a clean PDF version

Revised FKS518 REMS Assessment Plan

The revised FKS518 REMS assessment plan must include, but is not limited to, the following metrics. (additions are noted with underline and deletions with ~~strikethrough~~

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

1. Program Outreach and Communication

a. REMS Communication Plan Activities (*provide data for 18-month report only)
   i. *Number of healthcare providers (stratified by specialty) targeted by the REMS
   ii. *Number of professional societies targeted, and which professional societies reported distribution of the REMS letter to their respective members

iii. *REMS Letters: A summary that includes the following information, stratified by distribution waves (i.e., date distributed):
    1. Total number and percentage of hardcopy *REMS Letter for Healthcare Providers* mailed, returned, and resent after obtaining correct address
    2. Total number and percentage of *REMS Letter for Professional Societies* 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.
iv. Number and specialty of prescribers who received the *Patient Guide*
v. Dates and names of the key Professional Meetings attended and corresponding information on the REMS materials displayed and/or distributed

2. Program Implementation and Operations

a. Program Implementation (*Provide data for 18-month report only)
    i. *Date of first commercial availability of [PROPRIETARY NAME®]
    ii. *Date when the REMS website went live
    iii. Number of total visits and unique visits to the REMS website
    iv. Number and type of REMS materials downloaded or accessed
b. Utilization Data
    i. [PROPRIETARY NAME®] utilization information including but not limited to indication and type of healthcare provider (e.g., endocrinologists, rheumatologists, obstetricians/gynecologists, primary care physicians, oncologists, urologists)

3. Knowledge

a. Evaluation of healthcare providers' knowledge:
    i. An evaluation of healthcare providers' understanding of the risk of severe hypocalcemia in patients with advanced chronic kidney disease via analysis of assessment survey results, stratified by healthcare professional specialty (e.g., endocrinologists, rheumatologists, obstetricians/gynecologists, primary care physicians, oncologists, urologists)
    ii. An evaluation of healthcare providers' understanding of the need to assess for presence of CKD-MBD before initiating [PROPRIETARY NAME®], stratified by healthcare provider specialty
    iii. An evaluation of healthcare providers' understanding of the requirement to give each patient a copy of the *Patient Guide* via analysis of assessment survey results

4. Health Outcomes and/or Surrogates of Health Outcomes

a. Safety Surveillance:

i. A summary and analysis of all post-marketing case reports of severe hypocalcemia associated with [PROPRIETARY NAME®], stratified by kidney function

5. Overall Assessment of REMS Effectiveness

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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