Summary Review Memorandum

Date	See Electronic Stamp Date
From	Sabiha Khan, MD (Clinical Reviewer, OTBB) Michelle Luo, MD, PhD (CTL, CDTL, OTBB) Theresa Kehoe, MD (Division Signatory, DGE) Christy Osgood, MD (Division Signatory, DO1)
Subject	Request for Approval for Interchangeability after Provisional Determination - Summary Review of Amendment to BLA 761398/Original 2
Application Type	351(k) BLA
BLA/Supplement Number	761398/Original 2
Received Date	April 29, 2025
Target Action Date	October 29, 2025
Division/Office	Division of General Endocrinology/Office of Cardiology, Hematology, Endocrinology, and Nephrology Division of Oncology 1/Office of Oncologic Disease
Proprietary Name	Conexxence (proposed interchangeable biosimilar to US-licensed Prolia (US-Prolia)); and Bomyntra (proposed interchangeable biosimilar to US-licensed Xgeva (US-Xgeva))
Proper Name	denosumab-bnht
Product Code	FKS518
Reference Product	US-Prolia/Xgeva (denosumab)
Pharmacologic Class	Receptor Activator of Nuclear Factor Kappa B (RANK) Ligand (RANKL) Inhibitor
Applicant	Fresenius Kabi USA, LLC
Approved Indication(s)	Conexxence (proposed interchangeable biosimilar to US-Prolia): • Treatment of postmenopausal women with osteoporosis at high risk for fracture defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, denosumab reduces the incidence of vertebral, nonvertebral, and hip fractures. • Treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. • Treatment of glucocorticoid-induced osteoporosis in men and women at high risk for fracture who are

	either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months. High risk of fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy. • Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer. In these patients denosumab also reduced the incidence of vertebral fractures. • Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer. Bomyntra (proposed interchangeable biosimilar to US-Xgeva): • Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors. • Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity. • Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy.
Purpose of the Submission	Approval of Conexxence (denosumab-bnht) as interchangeable with US-Prolia (denosumab) and Bomyntra (denosumab-bnht) as interchangeable with US-Xgeva (denosumab) as follows per the provisional determination letter dated March 25, 2025: • Conexxence (denosumab- bnht) 60 mg/mL injection for subcutaneous use in a single-dose prefilled syringe (PFS) as interchangeable with US-Prolia (denosumab) 60 mg/mL injection for subcutaneous use in a PFS, and • Bomyntra (denosumab- bnht) 120 mg/1.7 mL (70mg/mL) injection for subcutaneous use in a single-dose vial (vial) and in a PFS as interchangeable with US-Xgeva (denosumab) 120 mg/1.7 mL (70mg/mL) injection for subcutaneous use in a vial.
New Indication(s) and/or Population(s)	N/A
New Dosing Regimen(s)	N/A

Recommendation on Regulatory Action	Approval of: • Conexxence (denosumab- bnht) 60 mg/mL injection for subcutaneous use in a PFS as interchangeable with US-Prolia (denosumab) 60 mg/mL injection for subcutaneous use in a PFS, and • Bomyntra (denosumab- bnht)120 mg/1.7 mL (70mg/mL) injection for subcutaneous use in a vial and in a PFS as interchangeable with US-Xgeva (denosumab) 120 mg/1.7 mL (70mg/mL) injection for subcutaneous use in a vial.

1. Background/Regulatory History

The subject of this review is the amendment submitted on April 29, 2025, to BLA 761398/Original 2 to seek approval for interchangeability of all products under the application that previously received a provisional determination on March 25, 2025.

On March 24, 2024, Fresenius Kabi USA, LLC (Applicant) submitted a Biologics License Application (BLA) 761398 under section 351(k) of the Public Health Service (PHS) Act seeking licensure of Conexxence (denosumab-bnht) injection and Bomyntra (denosumab-bnht) injection, product code FKS518, as an interchangeable biosimilar product as follows:

- Conexxence (denosumab-bnht) injection 60 mg/mL in a single-dose prefilled syringe (PFS) for subcutaneous use as an interchangeable biosimilar with US-Prolia (denosumab) 60 mg/mL in a PFS for subcutaneous use, and
- Bomyntra (denosumab-bnht) injection 120 mg/1.7 mL (70mg/mL) in a single-dose vial (vial) and in a PFS for subcutaneous use as an interchangeable biosimilar with US-Xgeva (denosumab) 120 mg/1.7 mL (70mg/mL) in a vial for subcutaneous use.

The data and information submitted in the original BLA supported licensure of Conexxence and Bomyntra as biosimilar products. The Applicant included a scientific justification that Conexxence and Bomyntra will produce the same clinical result in any given patient for each condition of use for which licensure is sought and for which US-Prolia and US-Xgeva have been approved, a scientific justification for extrapolating data and information to support licensure of Conexxence and Bomyntra as interchangeable for which licensure is sought and for which US-Prolia and US-Xgeva have been previously approved, and use-related risk analyses and comparative analyses for the PFS platform. The data and information in the BLA demonstrated that Conexxence and Bomyntra can be expected to produce the same clinical result as US-Prolia and US-Xgeva, respectively, in any given patient, and that the risk in terms of safety or diminished efficacy of alternating or switching between the use of Conexxence and US-Prolia or Bomyntra and US-Xgeva is not greater than the risk of using US-Prolia or US-Xgeva without such alternation or switch.

After reviewing BLA 761398, FDA did not identify any deficiencies that would justify a complete response action. FDA considered whether any unexpired first interchangeable exclusivity precluded approval of any products in the BLA as interchangeable. Conexxence and Bomyntra could not be approved as interchangeable at that time due to unexpired first interchangeable exclusivity for Jubbonti (denosumab-bbdz) injection 60 mg/mL for subcutaneous use and Wyost (denosumab-bbdz) injection 120 mg/1.7 mL (70 mg/mL) for subcutaneous use. Refer to the Purple Book at https://purplebooksearch.fda.gov for more information about unexpired first interchangeable exclusivity.

Therefore, BLA 761398 was administratively split to facilitate the following:

- An approval action for BLA 761398/Original 1:
  - Conexxence (denosumab-bnht) 60 mg/mL injection for subcutaneous use in a PFS as biosimilar to US-Prolia (denosumab) 60 mg/mL injection for subcutaneous use in a PFS,
  - Bomyntra (denosumab-bnht) 120 mg/1.7 mL (70 mg/mL) injection for subcutaneous use in a vial and in a PFS as biosimilar to US-Xgeva (denosumab) 120 mg/1.7 mL (70 mg/mL) injection for subcutaneous use in a vial.

- A provisional determination for BLA 761398/Original 2:
  - Conexxence (denosumab-bnht) 60 mg/mL injection for subcutaneous use in a PFS meets the applicable standards for interchangeability with US-Prolia (denosumab) 60 mg/mL injection for subcutaneous use in a PFS,
  - Bomyntra (denosumab-bnht) 120 mg/1.7 mL (70 mg/mL) injection for subcutaneous use in a vial and in a PFS meets the applicable standards for interchangeability with US-Xgeva (denosumab) 120 mg/1.7 mL (70 mg/mL) injection for subcutaneous use in a vial.

The “Biosimilar Multidisciplinary Evaluation and Review” (BMER) documenting the Agency’s review of BLA 761398 dated March 25, 2025, is incorporated herein by reference.

BLA 761398/Original 1 received an approval letter dated March 25, 2025, and BLA 761398/Original 2 received a provisional determination letter dated March 25, 2025. The provisional determination letter instructed the Applicant to submit an amendment no more than six months prior to the date it believed that the application would be eligible for approval.

2. Request for Approval

To obtain approval of Conexxence (denosumab-bnht) 60 mg/mL injection for subcutaneous use in a PFS and Bomyntra (denosumab-bnht) 120 mg/1.7 mL (70 mg/mL) injection for subcutaneous use in a vial and in a PFS as interchangeable products, the Applicant submitted an amendment, “AMENDMENT: REQUEST FOR APPROVAL SEEKING INTERCHANGEABILITY CLAIM FOR CONEXXENCE AND BOMYNTRA (DENOSUMAB-BNHT,” under BLA 761398/Original 2 on April 29, 2025, which is the subject of this review.

3. Summary Recommendations

The provisional determination letter issued March 25, 2025, states, “[i]n addition to a

safety update, the amendment should also identify changes, if any, in the application, i.e., updated labeling; chemistry, manufacturing, and controls data; and risk evaluation and mitigation strategy (REMS)."

In its Request for Approval dated April 29, 2025, the Applicant stated there have been no safety updates and no CMC changes for Conexxence and Bomyntra since approval of the original BLA and noted there were no unsolicited changes made to the approved labeling except for one minor change made in agreement with the Agency. All facilities remain compliant to support approval.

The Applicant submitted updated labeling on September 10 and September 18, 2025, in response to an Information Request (IR) seeking updated labeling given the changes to the labeling for Prolia on May 22, 2025, and Xgeva on May 30, 2025.

On July 16, 2025, the Applicant submitted a Periodic Adverse Experience Report (PADER) for Conexxence and Bomyntra covering the safety reporting period from March 25, 2025, to June 24, 2025. The review team identified no safety concerns in their review of the PADER.

The review team considered the changes and updates to the application and determined that they do not change our previous determination that BLA 761398/Original 2 meets the applicable standards for interchangeability.

4. Labeling

On May 22, 2025, FDA approved BLA 125320/S-219 for US-Prolia updating subsection 8.4 Pediatric Use in the USPI. On May 30, 2025, FDA approved BLA 125320/S-222 for US-Xgeva updating section 2 Dosage and Administration in the USPI as well as carton and container labeling. The Applicant submitted revised draft branded product and unbranded biological product labeling for Conexxence and Bomyntra that incorporated relevant information from the updated Prolia and Xgeva labeling, respectively, with appropriate modifications. The review team determined that the proposed labeling for Conexxence and Bomyntra is compliant with the Physician Labeling Rule (PLR) and the Pregnancy and Lactation Labeling Rule (PLLR), is clinically meaningful and scientifically accurate, and conveys the essential scientific information needed for safe and effective use of the product.

The final branded product and unbranded biological product labeling for both Conexxence and Bomyntra will be attached to the approval letter.

5. Pediatrics

Under the Pediatric Research Equity Act (PREA) (section 505B of the FD&C Act), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain a pediatric assessment to support dosing, safety, and effectiveness of the product for the claimed

indication unless this requirement is waived, deferred, or inapplicable. Section 505B(l) of the FD&C Act provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a "new active ingredient" for purposes of PREA, and a pediatric assessment is generally required unless waived or deferred or inapplicable. Under the statute, a biological product that is interchangeable with the reference product is not considered to have a "new active ingredient" for purposes of PREA.

At the time BLA 761398/Original 1 was approved on March 25, 2025, a PREA PMR was issued:

4819-1 Provide an assessment of Conexxence (denosumab-bnht) for the treatment of glucocorticoid-induced osteoporosis in pediatric patients 5 to 17 years of age.

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The Applicant submitted revised labeling to align with changes to the US-Prolia labeling updates approved on May 22, 2025, which updated subsection 8.4 Pediatric Use in the USPI. The updated labeling states that safety and effectiveness of Conexxence have not been established in pediatric patients, including for patients aged 5-17 years with glucocorticoid-induced osteoporosis (GIOP). The Applicant fulfilled PREA requirements for this indication by including the relevant pediatric information in the labeling.

PeRC discussed this application on October 7, 2025, and agreed this product is assessed in pediatric patients 5 to 17 years of age for the GIOP indication and that PREA PMR 4819-1 is fulfilled.

6. REMS and Postmarketing Requirements and Commitments

6.1. Recommendations for Risk Evaluation and Mitigation Strategies

US-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 US-Prolia REMS consists of a communication plan (CP) and timetable for submission of assessments.

Conexxence was approved with a REMS on March 25, 2025, and the Conexxence REMS is comparable to the US-Prolia REMS and is designed to communicate the same key risk messages and achieve the same level of patient safety. The requirements of the Conexxence REMS also apply to any unbranded denosumab-bnht distributed by the Applicant.

The Conexxence REMS goal and objective are:

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

dependent patients, associated with Conexxence. The following describes the objective associated with the REMS:

Objective 1: Inform healthcare providers on:

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

The REMS elements consist of a Communication plan (CP) and timetable for submission of assessments.

The Communication Plan elements include:

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

Timetable for submission of assessments is at 18 months, 3 years, and 7 years from the date of the initial approval of the REMS.

6.2 Postmarketing Requirements and Commitments

The Applicant has fulfilled the following PMR:

4819-1: Provide an assessment of Conexxence (denosumab-bnht) for the treatment of glucocorticoid-induced osteoporosis in pediatric patients 5 to 17 years of age.

7. Recommended Regulatory Action

The data and information in BLA 761398/Original 2, including the information submitted by the Applicant with this amendment, are sufficient to maintain FDA's determination that Conexxence and Bomyntra can be expected to produce the same clinical result as US-Prolia and US-Xgeva in any given patient, and that the risk in terms of safety or diminished efficacy of alternating or switching between use of Conexxence and Bomyntra is not greater than the use of US-Prolia and US-Xgeva without such alternation or switch. The information submitted by the Applicant, including adequate justification for extrapolation of data and information, demonstrates that:

- Conexxence (denosumab-bnht) 60 mg/mL injection for subcutaneous use in a PFS is interchangeable with US-Prolia 60 mg/mL injection for subcutaneous use in a PFS, and
- Bomyntra (denosumab-bnht) 120 mg/1.7 mL (70 mg/mL) injection for subcutaneous use in a vial and in a PFS is interchangeable with US-Xgeva 120 mg/1.7 mL (70 mg/mL) injection for subcutaneous use in a vial.

These Conexxence and Bomyntra (denosumab- bnht) products have met the statutory interchangeability requirements for the following indications for which US-Prolia and US-Xgeva have been previously approved:

Conexxence:

- Treatment of postmenopausal women with osteoporosis at high risk for fracture defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, denosumab reduces the incidence of vertebral, nonvertebral, and hip fractures.
- Treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy.
- Treatment of glucocorticoid-induced osteoporosis in men and women at high risk for fracture who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months. High risk of fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy.
- Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer. In these patients denosumab also reduced the incidence of vertebral fractures.
- Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer.

Bomyntra:

- Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors.
- Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity.
- Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy.

As noted in the Purple Book (https://purplebooksearch.fda.gov), the applicable first interchangeable exclusivity expiration dates are:

- Jubbonti (denosumab-bbdz) 60 mg/mL injection for subcutaneous use: October 29, 2025
- Wyost (denosumab-bbdz) 120 mg/1.7 mL (70 mg/mL) injection for subcutaneous use: October 29, 2025

The recommended regulatory action is approval of:

- Conexxence (denosumab-bnht) 60 mg/mL injection for subcutaneous use in a PFS is interchangeable with US-Prolia (denosumab) 60 mg/mL injection for subcutaneous use in a PFS, and
- Bomyntra (denosumab-bnht) 120 mg/1.7 mL (70 mg/mL) injection for subcutaneous use in a vial and in a single-dose PFS is interchangeable with US-Xgeva (denosumab) 120 mg/1.7 mL (70 mg/mL) injection for subcutaneous use in a vial.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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