BLA 761398/Original 1

BLA APPROVAL

Fresenius Kabi USA, LLC
Attention: Navayath Shobana, Ph.D.
Senior Director, Regulatory Affairs
Three Corporate Drive
Lake Zurich, IL 60047

Dear Dr. Shobana:

Please refer to your biologics license application (BLA) dated and received March 25, 2024, and your amendments, submitted under section 351(k) of the Public Health Service Act for Conexxence (denosumab-bnht) injection and Bomyntra (denosumab-bnht) injection.

This BLA seeks licensure of:

- Conexxence (denosumab-bnht) 60 mg/mL injection for subcutaneous use in a single-dose prefilled syringe (PFS) as (b) (4) biosimilar with US-Prolia (denosumab) 60 mg/mL injection for subcutaneous use in a single-dose PFS, and

- Bomyntra (denosumab-bnht) 120 mg/1.7 mL (70 mg/mL) injection for subcutaneous use in a single-dose vial and single-dose PFS as (b) (4) biosimilars with US-Xgeva (denosumab), 120 mg/1.7 mL (70 mg/mL) injection for subcutaneous use in a single-dose vial.

For administrative purposes, we have split BLA 761398 as follows:

- BLA 761398/Original 1 - biosimilarity (b) (4)

The subject of this action letter is BLA 761398/Original 1. (b) (4) (b) (4)

All future submissions to this BLA should specify the BLA number and the Original number to which each submission pertains.

LICENSING

We have approved your BLA 761398/Original 1 for Conexxence (denosumab-bnht) and Bomyntra (denosumab-bnht) as biosimilar products effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Conexxence

and Bomyntra under your existing Department of Health and Human Services U.S. License No. 2146.

Conexxence is indicated for:

- 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 of 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 is indicated for:

- 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.

This BLA also provides for unbranded biological product labeling for Denosumab-bnht.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture denosumab-bnht drug substance [redacted] (b) (4) The final formulated product will be manufactured, and filled [redacted] (b) (4) The final labeling and secondary packaging will be performed at Fresenius Kabi Austria GmbH, Werndorf, Austria. You may label your product with the proprietary name, Conexxence, and will market it in 60 mg/1 mL (60 mg/mL) single-dose prefilled syringe, injection. You may label your product with the proprietary name, Bomyntra, and will market it in 120 mg/1.7 mL (70 mg/mL) single-dose vial, injection and single-dose prefilled syringe, injection.

DATING PERIOD

The dating periods for Conexxence and Bomyntra shall be 30 months from the date of manufacture when stored at 5 ± 3 °C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be (b) (4) months from the date of manufacture when stored at [redacted] (b) (4) (b) (4) °C. Results of ongoing stability studies should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots.

We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Conexxence and Bomyntra to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of Conexxence and Bomyntra, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

APPROVAL AND LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*[2]

The SPL will be accessible via publicly available labeling repositories.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling submitted on March 19, 2025, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved BLA 761398/Original 1**." Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Bomyntra (denosumab-bnht)

- Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where resection is likely to result in severe morbidity

  At this time, we have determined that, with respect to giant cell tumor in pediatric patients who are not skeletally mature, no pediatric assessment will be required under PREA for your BLA. You have provided a pediatric assessment for skeletally mature adolescents with giant cell tumor in pediatric patients, and nothing is further required at this time.

- Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors

  At this time, we have determined that no pediatric assessment will be required under PREA for your BLA.

- Treatment of hypercalcemia of malignancy of refractory to bisphosphonate therapy

  At this time, we have determined that no pediatric assessment will be required under PREA for your BLA.

Conexxence (denosumab-bnht)

- 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 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

  At this time, we have determined that no pediatric assessment will be required under PREA for your BLA.

- Treatment of glucocorticoid-induced osteoporosis in men and women at high risk of fracture (pediatric population 0 to 4 years of age)

  At this time, we have determined that, with respect to glucocorticoid-induced osteoporosis in pediatric patients 0 to 4 years of age, no pediatric assessment will be required under PREA for your BLA. We are deferring the required pediatric assessment for pediatric patients 5 to 17 years and older. See Deferred Pediatric Assessment below.

Deferred Pediatric Assessments:
Your deferred pediatric assessment required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required postmarketing assessment. The status of this postmarketing assessment must be reported annually according to 21 CFR 601.28 and section 505B(a)(4)(B) of the Federal Food, Drug, and Cosmetic Act. This required assessment is listed below.

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.

Final Report Submission: 06/2026

Reports of this required pediatric postmarketing assessment must be submitted as a BLA or as a supplement to your approved BLA with the proposed labeling changes you believe are warranted based on the data derived from this assessment. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the Food Drug 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.

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Conexxence to ensure the benefits of the drug outweigh the risk of severe hypocalcemia in patients with advanced chronic kidney disease (CKD) including dialysis-dependent patients associated with Conexxence.

Your proposed REMS must also include the following:

Communication Plan: We have determined that a communication plan targeted to healthcare providers who are likely to prescribe Conexxence is necessary to ensure the benefits of the drug outweigh the risk. The communication plan provides for the dissemination of information about the risk of severe hypocalcemia in patients with advanced chronic kidney disease (CKD) including dialysis-dependent patients associated with Conexxence.

The communication plan must include, at minimum, the following:

- Dissemination of REMS Letters to healthcare providers and professional societies according to the timeframes listed in the REMS Document

- Dissemination of the Conexxence Patient Guide via professional meetings and field based medical representatives to be used as a patient counseling tool
- Maintain a Conexxence REMS website with all REMS materials

Your proposed REMS, submitted on March 25, 2024, amended and appended to this letter, is approved.

The REMS consists of a communication plan and a timetable for submission of assessments of the REMS.

Your REMS must be fully operational before you introduce Conexxence into interstate commerce.

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

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):

(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

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.

If the information provided in an assessment is insufficient to allow FDA to determine whether the REMS is meeting its goals or whether the REMS must be modified, FDA may require the submission of a new assessment plan that contains the metrics and/or methods necessary to make such a determination. Therefore, FDA strongly recommends obtaining FDA feedback on the details of your proposed assessment plan to ensure its success. To that end, we recommend that methodological approaches, study protocols, other analysis plans and assessment approaches used to assess a REMS program be submitted for FDA review as follows:

- Submit your proposed protocol for the healthcare providers' knowledge survey for FDA review.

Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

> **BLA 761398 REMS ASSESSMENT METHODOLOGY**
> **(**insert concise description of content in bold capital letters, e.g.,
> **REQUEST FOR REMS ASSESSMENT METHODOLOGY PROTOCOL REVIEW/ SURVEY METHODOLOGIES)**

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A). This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;

b) A determination of the implications of a change in the benefit-risk profile for the current REMS;

c) *If the new, proposed indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.

d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of the last assessment and if any modifications of the REMS have been proposed since that assessment.

e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.

f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing a REMS modification*, provide a rationale for why the REMS does not need to be modified.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

BLA 761398 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR BLA 761398/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 761398/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 761398/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR BLA 761398/S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISION FOR BLA 761398

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

As soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in Structured Product Labeling (SPL) format using the FDA automated drug registration and listing system (eLIST). Content of the REMS document must be identical to the approved REMS document. The SPL will be publicly available.

Information on submitting REMS in SPL format may be found in the guidance for industry *Providing Regulatory Submission in Electronic Format – Content of the Risk Evaluation and Mitigation Strategies Document Using Structured Product Labeling*.

For additional information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.[3]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

[21 CFR 601.12(f)(4)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80).

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA 3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4207
Silver Spring, MD 20903

[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

If you have any questions, contact Julie Van der Waag, Director, Project Management Staff, at (301) 796-1280 or julie.vanderwaag@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Theresa E. Kehoe, M.D.
Director
Division of General Endocrinology
Office of Cardiology, Hematology,
Endocrinology, and Nephrology
Office of New Drugs
Center for Drug Evaluation and Research

and

Sincerely,

{See appended electronic signature page}

Christy Osgood, M.D.
Associate Director for Therapeutics
Division of Oncology 1
Office of Oncologic Diseases
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:
Branded Product Labeling

- Content of Labeling
  - Prescribing Information
  - Medication Guide (Conexxence)
- Carton and Container Labeling
  - Bomyntra
  - Conexxence

Unbranded Biological Product Labeling

- Content of Labeling
  - Prescribing Information
  - Medication Guide (Conexxence)
- Carton and Container Labeling
  - Bomyntra
  - Conexxence
- Conexxence REMS

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/

THERESA E KEHOE
03/25/2025 10:24:27 AM

CHRISTY L OSGOOD
03/25/2025 10:25:15 AM