CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761398Orig1s000
761398Orig2s000

OTHER ACTION LETTERS

U.S. FOOD & DRUG ADMINISTRATION

BLA 761398/Original 2

PROVISIONAL DETERMINATION

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 (PHS) Act for Conexxence (denosumab-bnht) injection and Bomyntra (denosumab-bnht) injection.

BLA 761398 seeks licensure of:

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

This BLA proposes the use of Conexxence (denosumab-bnht) injection 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.

This BLA proposes the use of Bomyntra (denosumab-bnht) injection 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.

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

- BLA 761398/Original 1 – biosimilarity
- BLA 761398/Original 2 – interchangeability

The subject of this correspondence is BLA 761398/Original 2. A separate correspondence was issued for BLA 761398/Original 1.

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

We have completed a provisional review of this application, as amended. A final determination under sections 351(i) and 351(k) of the PHS Act that:

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

is currently subject to unexpired exclusivity for the first interchangeable biosimilar biological products, and thus may not be made before the exclusivity has expired. See section 351(k)(6) of the PHS Act. We have not identified any deficiencies that would

justify a complete response action at this time; however, we also cannot approve your application because of the unexpired first interchangeable exclusivity. We have therefore provisionally determined that your 351(k) application meets the interchangeability criteria under section 351(k) of the PHS Act.

This provisional determination is based upon information available to the Agency at this time (i.e., information in your application and that the manufacturing of the biological product complies with the standards established in the BLA as well as the requirements in applicable regulations). This determination is subject to change on the basis of any new information that may come to our attention.

To obtain approval of this application, submit an amendment no more than six months prior to the date you believe that your application will be eligible for approval. In your cover letter, clearly identify your amendment as **"REQUEST FOR APPROVAL"**. This amendment should provide the legal/regulatory basis for your request for approval and should include a copy of any relevant supporting documentation, as appropriate. In 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). If there are no changes, clearly state so in your cover letter. Any changes require our review before approval, and the goal date for our review will be set accordingly.

BLA 761398/Original 2 is not approved and Conexxence (denosumab-bnht) and Bomyntra (denosumab-bnht) cannot be legally marketed as interchangeable biosimilar products unless and until you have been notified in writing that BLA 761398/Original 2 is approved after any necessary additional review. Enclosed are the currently agreed upon labeling (text for the Prescribing Information, Medication Guide, Carton and Container labeling). If you believe that there are grounds for issuing the approval letter before the expiration of the exclusivity period, you should amend your application accordingly.

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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Refer to the "Required Pediatric Assessments" section of the correspondence for BLA 761398/Original 1.

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.

Refer to the "Risk Evaluation and Mitigation Strategy Requirements" section of the correspondence for BLA 761398/Original 1.

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, MD
Director
Division of General Endocrinology
Office of Cardiology, Hematology, Endocrinology and Nephrology
Office of New Drugs
Center for Drug Evaluation and Research

and

{See appended electronic signature page}

Christy Osgood, MD
Lead Physician
Division of Oncology Products 1
Office of Hematology and Oncology Products
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

138 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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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 10:09:02 AM

CHRISTY L OSGOOD
03/25/2025 10:25:32 AM