CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

761392Orig1s000
761392Orig2s000

Trade Name:	Ospomyv injection and Xbryk injection
Generic or Proper Name:	denosumab-dssb
Sponsor:	Samsung Bioepis Co., Ltd.
Approval Date:	Original 1: February 13, 2025 Original 2: October 29, 2025
Indication:	Ospomyv is indicated for treatment: • of postmenopausal women with osteoporosis at high risk for fracture • to increase bone mass in men with osteoporosis at high risk for fracture • of glucocorticoid-induced osteoporosis in men and women at high risk for fracture • to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer • to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer Xbryk 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.

CENTER FOR DRUG EVALUATION AND RESEARCH

761392Orig1s000
761392Orig2s000

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761392Orig1s000
761392Orig2s000

APPROVAL LETTER

BLA 761392/Original 2

BLA APPROVAL
FULFILLMENT OF POSTMARKETING REQUIREMENT

Samsung Bioepis Co., Ltd.
c/o Samsung Bioepis United States Inc
Attention: Yelena Vaydman, MS, RAC
Senior Manager, Regulatory Affairs
400 Frank W Burr Blvd
Glenpointe The Atrium, Suite #125
Teaneck, NJ 07666

Dear Yelena Vaydman:

Please refer to your biologics license application (BLA) received February 12, 2024, and your amendments, under section 351(k) of the Public Health Service Act for Ospomyv (denosumab-dssb) injection and Xbryk (denosumab-dssb) injection.

We acknowledge receipt of your amendment dated April 30, 2025, which constituted a request for approval following our February 12, 2025, provisional determination letter.

BLA 761392 initially provided for:

- Ospomyv (denosumab-dssb) injection 60 mg/mL for subcutaneous use in a single-dose prefilled syringe as biosimilar to and interchangeable with US-Prolia (denosumab) injection 60 mg/mL for subcutaneous use in a single-dose prefilled syringe, and

- Xbryk (denosumab-dssb) injection 120 mg/1.7 mL (70mg/mL) for subcutaneous use in a single-dose vial as biosimilar to and interchangeable with US-Xgeva (denosumab) injection 120 mg/1.7 mL (70mg/mL) for subcutaneous use in a single-dose vial.

For administrative purposes, we have designated BLA 761392 as follows:

- BLA 761392/Original 1 - biosimilarity
- BLA 761392/Original 2 – interchangeability

The subject of this action letter is BLA 761392/Original 2. A separate action letter was issued for BLA 761392/Original 1 on February 13, 2025.

LICENSING

We have approved your BLA 761392/Original 2 for Ospomyv (denosumab-dssb) and Xbryk (denosumab-dssb) as interchangeable biosimilar products effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Ospomyv and Xbryk, under your existing Department of Health and Human Services U.S. License No. 2046.

Ospomyv 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.

Xbryk 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-dssb.

MANUFACTURING LOCATIONS

For information regarding approved manufacturing locations, see the Manufacturing Locations section of the approval letter for BLA 761392/Original 1 dated

February 13, 2025, and all approval letters for supplements to BLA 761392/Original 1 that were issued prior to this letter, if applicable.

FDA LOT RELEASE

For information regarding FDA lot release, see the FDA Lot Release section of the approval letter for BLA 761392/Original 1 dated February 13, 2025.

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.

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.

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.

At this time, we have determined that no pediatric studies are required under PREA for BLA 761392/Original 2.

FULFILLMENT OF POSTMARKETING REQUIREMENT

[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.

We have received your submission dated September 9, 2025, containing the final report for the following postmarketing requirement listed in the February 13, 2025, approval letter for BLA 761392/Original 1.

4799-1 Provide an assessment of Ospomyv (denosumab-dssb) for the treatment of glucocorticoid-induced osteoporosis in pediatric patients 5 to 17 years of age.

Final Report Submission: 06/2026

We have reviewed your submission and conclude that the above requirement was fulfilled.

This closes your postmarketing requirement acknowledged in our February 13, 2025, letter. You are not required to report on the status of closed (released or fulfilled) PMR in your annual report required under 21 CFR 601.70.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Ospomyv was originally approved on February 13, 2025. The REMS consists of a communication plan and a timetable for submission of assessments of the REMS.

Your approved REMS is appended to this letter.

The timetable for submission of assessments of the REMS remains the same as that approved on February 13, 2025.

There are no changes to the REMS assessment plan described in our February 13, 2025 letter.

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 761392 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR BLA 761392
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 761392
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 761392

PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR BLA 761392
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 761392

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 a reminder, if you have not submitted the REMS document in Structured Product Labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), do so within 14 days from the date of this letter. 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 [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

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

Your product is a Part 3 combination product (21 CFR 3.2(e)); therefore, you must also comply with postmarketing safety reporting requirements for an approved combination product (21 CFR 4, Subpart B). Additional information on combination product postmarketing safety reporting is available at FDA.gov.

If you have any questions, contact Chau Nguyen, Regulatory Project Manager at chau.nguyen@fda.hhs.gov or (240)-402-0022.

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
Supervisory Associate Director
Division of Oncology 1
Office of Oncologic DiseasesOffice of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:
Branded Product Labeling
- Content of Labeling
  - Prescribing Information
  - Medication Guide (Ospomyv)

Unbranded Biological Product Labeling
- Content of Labeling
  - Prescribing Information
  - Medication Guide (Ospomyv)

Ospomyv 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
10/29/2025 11:16:08 AM

CHRISTY L OSGOOD
10/29/2025 12:56:36 PM

BLA 761392/Original 1

BLA APPROVAL

Samsung Bioepis Co., Ltd.
c/o Samsung Bioepis United States Inc.
Attention: Yelena Vaydman, MS, RAC
Senior Manager, Regulatory Affairs
Glenpointe The Atrium, Suite #125
400 Frank W Burr Blvd
Teaneck, NJ 07666

Dear Yelena Vaydman:

Please refer to your biologics license application (BLA) dated February 11, 2024, received February 12, 2024, and your amendments, under section 351(k) of the Public Health Service Act for Ospomyv (denosumab-dssb) injection and Xbryk (denosumab-dssb) injection.

This BLA seeks licensure of:

- Ospomyv (denosumab-dssb) injection 60 mg/mL in a single-dose prefilled syringe for subcutaneous use as an interchangeable biosimilar with US-Prolia (denosumab) 60 mg/mL in a single-dose prefilled syringe for subcutaneous use, and

- Xbryk (denosumab-dssb) injection 120 mg/1.7 mL (70mg/mL) in a single-dose vial for subcutaneous use as an interchangeable biosimilar with US-Xgeva (denosumab) 120 mg/1.7 mL (70mg/mL) in a single-dose vial for subcutaneous use.

For administrative purposes, we have split BLA 761392 as follows:

- BLA 761392/Original 1 – biosimilarity
- BLA 761392/Original 2 – interchangeability

The subject of this correspondence is BLA 761392/Original 1. A separate correspondence will be issued for BLA 761392/Original 2.

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

LICENSING

We have approved your BLA 761392/Original 1 for Ospomyv (denosumab-dssb) and Xbryk (denosumab-dssb) as biosimilar products effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Ospomyv and Xbryk, under your existing Department of Health and Human Services U.S. License No. 2046.

Ospomyv 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.

Xbryk 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-dssb.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture denosumab-dssb drug substance at Samsung Biologics in 300, Songdo bio-daero, Yeonsu-gu, Incheon, 21987, Republic of Korea. The final formulated denosumab-dssb injection 60 mg/mL in a single-dose prefilled syringe will be manufactured and filled at (b) (4) The final formulated denosumab-dssb injection 120 mg/1.7 mL (70mg/mL) in a single-dose vial will be manufactured, filled, labeled, and packaged at Samsung Biologics, 300, Songdo bio-daero, Yeonsu-gu, Incheon, 21987, Republic of Korea. You may label your product with the proprietary name, Ospomyv, and market it in a 60 mg/mL single-dose prefilled syringe for subcutaneous use. You may label your product with the proprietary name, Xbyrk, and market it in a 120 mg/1.7 mL (70mg/mL) single-dose vial for subcutaneous use.

DATING PERIOD

The dating period for Ospomyv (denosumab-dssb) injection shall be 36 months from the date of manufacture when stored at 2 - 8 °C protected from light. The dating period for Xbryk (denosumab-dssb) injection shall be 36 months from the date of manufacture when stored at 2 - 8 °C protected from light.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 (b) (4).

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Ospomyv (denosumab-dssb) and Xbryk (denosumab-dssb) and each kit component 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 Ospomyv and Xbryk, 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, 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 761392**." 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.

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[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.

Xbryk (denosumab-dssb)

- 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 (0 to 12 years of age), no pediatric assessment will be required under PREA for your BLA. You have provided a pediatric assessment for giant cell tumor in pediatric patients 12 years to < 17 years of age, 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.

Ospomyv (denosumab-dssb)

- 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, and
- 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

  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.

4799-1 Provide an assessment of Ospomyv (denosumab-dssb) 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 Ospomyv 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 Ospomyv.

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 Ospomyv 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 Ospomyv.

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

Your proposed REMS, submitted on February 11, 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 Ospomyv into interstate commerce.

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

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

Outreach and Communication

1. REMS Communication Plan Activities (*provide data for the 18-month report only):
    a. *Number of Healthcare Providers (HCPs) (stratified by specialty) targeted by the REMS
    b. *Number of professional societies targeted, and which professional societies reported distribution of the REMS letter to their respective members
    c. *REMS Letters: A summary that includes the following information stratified by distribution waves (i.e., date distributed):
        i. Total number and percentage of hardcopy **REMS Letters for Healthcare Providers** mailed, returned, and resent after obtaining updated 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
    d. Number and specialty of prescribers who received the **Patient Guide**
    e. Date and name of the key professional meetings attended and corresponding information on the REMS materials displayed and/or distributed

Implementation and Operations

2. Program Implementation (*provide data for the 18-month report only):

a. *Date of first commercial availability of Ospomyv
b. *Date when the REMS Website went live
c. Number of total visits and unique visits to the REMS Website
d. Number and type of REMS materials downloaded or accessed

3. Utilization Data:
    a. Ospomyv utilization information including but not limited to indication and type of HCP (i.e., endocrinologist, general practitioner, internist, etc.)

Knowledge

4. Evaluation of Healthcare Provider's Knowledge:
    a. An evaluation of HCPs' understanding of the risks of severe hypocalcemia in patients with advanced chronic kidney disease via analysis of assessment survey results; and stratify results by HCP specialty (e.g., endocrinologist, rheumatologist, primary care provider)
    b. An evaluation of HCPs' understanding of the need to assess for presence of chronic kidney disease-mineral bone disorder (CKD-MBD) before initiating Ospomyv and stratify results by HCP specialty
    c. An evaluation of HCPs' understanding of the requirement to give each patient a copy of the **Patient Guide** via analysis of assessment surveys results

Health Outcomes and/or Surrogates of Health Outcomes

5. Safety Surveillance:
    a. A summary and analysis of all postmarketing case reports of severe hypocalcemia associated with Ospomyv, stratified by kidney function

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 1 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 within 90 days of this letter.

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 761392 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 761392 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR BLA 761392
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 761392
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 761392
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR BLA 761392
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 761392

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 [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]

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

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

Your product is a Part 3 combination product (21 CFR 3.2(e)); therefore, you must also comply with postmarketing safety reporting requirements for an approved combination product (21 CFR 4, Subpart B). Additional information on combination product postmarketing safety reporting is available at FDA.gov.

If you have any questions, contact Jennifer Johnson, Senior Regulatory Health Project Manager, at (301) 796-2194 or jennifer.johnson@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
Supervisory Associate Director
Division of Oncology 1
Office of Oncologic DiseasesOffice of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:
Branded Product Labeling

- Content of Labeling
  - Prescribing Information
  - Medication Guide (Ospomyv)
- Carton and Container Labeling
  - Ospomyv
  - Xbryk

Unbranded Biological Product Labeling

- Content of Labeling
  - Prescribing Information
  - Medication Guide (Ospomyv)
- Carton and Container Labeling
  - Ospomyv
  - Xbryk

Ospomyv 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
02/12/2025 06:30:14 PM

CHRISTY L OSGOOD
02/13/2025 09:14:14 AM