



BLA 125320/S-217

## SUPPLEMENT APPROVAL

Amgen Inc.  
Attention: Dohan Weeraratne, MS  
Manager, Regulatory Affairs  
One Amgen Center Drive  
Mail Stop: 38-4D  
Thousand Oaks, CA 91320-1799

Dear Dohan Weeraratne:

Please refer to your supplemental biologics license application (sBLA), dated and received February 2, 2024, and your amendment, submitted under section 351(a) of the Public Health Service Act for Prolia (denosumab) injection.

This Prior Approval sBLA provides for proposed modifications to the approved Prolia risk evaluation and mitigation strategy (REMS). This supplement is in response to our January 19, 2024, REMS Modification Notification letter.

### **RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENT**

The REMS for Prolia was originally approved on June 1, 2010, and the most recent REMS modification was approved on January 19, 2024. The REMS consists of a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS.

In order to ensure the benefits of Prolia outweigh its risks and to minimize burden on the healthcare delivery system of complying with the REMS, we determined that you were required to make the REMS modifications outlined in our REMS Modification Notification letter dated January 19, 2024.

**Medication Guide:** We have determined that maintaining the Medication Guide as part of the approved labeling is adequate to address the serious and significant public health concern and meets the standard in 21 CFR 208. Therefore, it is no longer necessary to include the Medication Guide as an element of the approved REMS to ensure that the benefits of Prolia outweigh its risks. The Medication Guide will continue to be part of the approved labeling in accordance with 21 CFR 208. Like other labeling, Medication Guides are subject to the safety labeling change provisions of section 505(o)(4) of the FDCA.

Your proposed modified REMS, submitted on February 2, 2024, amended and appended to this letter, is approved. The modified REMS consists of a communication plan and a timetable for submission of assessments of the REMS.

The timetable for submission of assessments of the REMS must be revised to include submission of assessments at 18 months, 3 years, and 7 years following approval of the modified REMS.

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

For each metric, provide the 2 previous, current, and cumulative reporting periods (if applicable), unless otherwise noted.

### **Program Outreach and Communication**

1. REMS Communication Plan Activities (\*provide data for the 18-month report only)
  - a. \*Number of healthcare providers (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 Letter 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.

### **Program Implementation and Operations**

2. Program Implementation (\*Provide data for 18-month report only)
  - a. \*Launch date of revised Communication Plan
  - b. Number of total visits and unique visits to the REMS website
  - c. Number and type of REMS materials downloaded or accessed.
3. Utilization Data
  - a. PROLIA utilization information including but not limited to indication and type of healthcare provider (i.e., endocrinologist, general practitioner, internist, etc.)

## Knowledge

4. Evaluation of healthcare provider's knowledge
  - a. 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; and stratify results by healthcare provider specialty (e.g., endocrinologist, rheumatologist, primary care provider)
  - b. An evaluation of healthcare providers' understanding of the need to assess for presence of CKD-MBD before initiating PROLIA and stratify results by healthcare provider specialty.
  - c. An evaluation of healthcare providers' 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 post marketing case reports of hypocalcemia associated with PROLIA, stratified by kidney function.
6. 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.

We strongly recommend obtaining FDA feedback on the details of your proposed assessment plan to ensure its success. To that end, we recommend that you 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: **"REQUEST FOR REMS ASSESSMENT METHODOLOGY PROTOCOL REVIEW/ SURVEY METHODOLOGIES"** in bold capital letters, at the **top** of your cover letter **and** at the **top** of the first page of the main submission document.

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) of the FDCA. 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 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 that 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 REMS modifications,* provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted.

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 125320 REMS ASSESSMENT METHODOLOGY**

(insert concise description of content in bold capital letters, e.g.,  
**ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES,  
AUDIT PLAN, DRUG USE STUDY**)

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 125320 REMS ASSESSMENT**

*or*

**NEW SUPPLEMENT FOR BLA 125320  
CHANGES BEING EFFECTED IN 30 DAYS  
PROPOSED MINOR REMS MODIFICATION**

*or*

**NEW SUPPLEMENT FOR BLA 125320  
PRIOR APPROVAL SUPPLEMENT  
PROPOSED MAJOR REMS MODIFICATION**

*or*

**NEW SUPPLEMENT FOR BLA 125320  
PRIOR APPROVAL SUPPLEMENT  
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING  
CHANGES SUBMITTED IN SUPPLEMENT XXX**

*or*

**NEW SUPPLEMENT (NEW INDICATION FOR USE)  
FOR BLA 125320  
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 REVISIONS FOR BLA 125320**

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, or website screenshots are only in PDF format, they may be submitted as such, but Word format is preferred.

### **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 more information on submitting REMS in SPL format, please email [FDAREMSwebsite@fda.hhs.gov](mailto:FDAREMSwebsite@fda.hhs.gov).

### **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

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](http://FDA.gov).

If you have any questions, call Elisabeth Hanan, Chief, Project Management Staff, at 240-402-0350.

Sincerely,

*{See appended electronic signature page}*

Marina Zemskova, MD  
Deputy Director for Safety  
Division of General Endocrinology  
Office of Cardiology, Hematology, Endocrinology,  
and Nephrology  
Center for Drug Evaluation and Research

ENCLOSURES:

- REMS
  - Prolia REMS Document
  - Prolia REMS Patient Guide
  - Prolia REMS Letter for Healthcare Providers
  - Prolia REMS Letter for Professional Societies
  - Prolia REMS Website

-----  
**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/  
-----

MARINA ZEMSKOVA  
03/05/2024 08:59:34 AM