Hogan Lovells US LLP
Columbia Square
555 Thirteenth Street, NW
Washington, DC 20004
T +1 202 637 5600
F +1 202 637 5910
www.hoganlovells.com

August 1, 2019

BY ELECTRONIC SUBMISSION

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Docket No. FDA-2019-P-1818
Comments in Response to Public Citizen's Health Research Group's Citizen Petition Regarding Prolia® (denosumab)

Dear Sir or Madam:

Amgen Inc. (Amgen), through undersigned counsel, submits the following comments in response to the above-referenced petition (the Petition) submitted by Public Citizen (the Petitioner) on April 16, 2019.[1] Amgen manufactures and markets Prolia® (denosumab) 60 mg/mL solution for subcutaneous injection under biologics license application (BLA) 125320, which was first approved by the Food and Drug Administration (FDA or the Agency) in 2010.

In its Petition, Public Citizen requests that FDA take the following actions:

(1) add a Boxed Warning to the product labeling of Prolia® regarding the risk of "multiple vertebral fractures" (MVF) following drug discontinuation; and

(2) modify the approved Risk Evaluation and Mitigation Strategy (REMS) currently in place for Prolia® to require distribution of updated REMS documents and to require that the updated Patient Brochure be provided to the patient with each dose.[2]

As described in greater detail below, Amgen respectfully requests that FDA deny the Petitioner's requested actions.

[1] Petition on behalf of Public Citizen and Public Citizen's Health Research Group, Docket No. FDA-2019-P-1818 (April 16, 2019).

[2] *Id.* at 1.

Amgen's mission is to serve patients, and patient safety is a priority. As part of its comprehensive pharmacovigilance activities, Amgen's Global Patient Safety department routinely collects and evaluates all information regarding the safety of its pharmaceutical products, including Prolia®. Amgen provides complete product benefit/risk information to FDA and other regulatory agencies in accordance with applicable law and regulations, and works collaboratively with these regulatory agencies to timely and effectively communicate the information to patients and healthcare practitioners, as appropriate.

In the case of Prolia®, Amgen has communicated to FDA the available information that has informed Amgen's understanding of the risk of MVF following discontinuation of Prolia® treatment. In 2016, Amgen submitted a supplement to propose labeling changes to address this risk. In turn, FDA reviewed this information, and FDA and Amgen agreed to add to the Prolia® Package Insert and Medication Guide a warning and precaution and additional information about the risk of MVF following treatment discontinuation to inform both healthcare practitioners and patients. These labeling changes reflect both Amgen and FDA's determination that the benefits of Prolia® in its approved indications continue to outweigh its known risks. Specifically, the Agency determined that the risk of MVF following discontinuation of Prolia® could be appropriately addressed through the current Package Insert and Medication Guide, without additional risk minimization and mitigation measures, such as the addition of a Boxed Warning or modifications to the approved REMS, as requested by the Petitioner. The Petition contains no new information that has not already been reviewed by the Agency and Amgen, and no evidence that the risk of MVF following treatment discontinuation is not appropriately communicated through the existing labeling.

I. BACKGROUND

A. Prolia® (denosumab) Approval History

On June 1, 2010, FDA approved BLA 125320 for Prolia® (denosumab) 60 mg/mL solution for subcutaneous injection. At that time, Prolia® was approved for "the 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."[3] FDA subsequently approved several efficacy supplements to BLA 125320 to provide for the following additional indications:

- 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;

[3] Package Insert, BLA 125320 (June 1, 2010).

- Treatment for 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 of 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months. High risk of 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 to increase bone mass in men at high risk of fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer. In these patients Prolia also reduced the incidence of vertebral fractures; and

- Treatment to increase bone mass in women at high risk of fracture receiving adjuvant aromatase inhibitor therapy for breast cancer.[4]

Prolia® is distributed as a single prefilled syringe containing 60 mg of denosumab per 1 mL of solution. The recommended dose of Prolia® is 60 mg administered as a single subcutaneous injection once every 6 months.[5]

B. Citizen Petition Submitted By Public Citizen

Public Citizen submitted its Petition on April 16, 2019. The Petition acknowledges that FDA has already approved a labeling supplement to include important safety information regarding the risk of MVF following discontinuation of Prolia®.[6] Nevertheless, the Petitioner asserts, without support, that "many healthcare providers and patients likely remain unaware" of these risks.[7]

For that reason, the Petitioner requests that FDA require two major changes to the Prolia® labeling. First, the Petitioner asks that FDA add a Boxed Warning to the Prolia® Package Insert to describe the risk of MVF following treatment discontinuation.[8] The Boxed Warning language suggested by the Petitioner differs in certain regards from the current Warning in Section 5.6.[9] The Petitioner also requests that FDA require "conforming changes" to other sections of the Prolia® Package Insert.

---

[4] Package Insert, BLA 125320 (July 26, 2019), *available at* https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125320s198lbl.pdf.

[5] *Id.* at Section 2.2.

[6] Petition at 5-6.

[7] *Id.* at 6.

[8] *Id.* at 17.

[9] *Id.*

Second, the Petitioner requests that the risk of MVF following discontinuation of Prolia® be included in existing REMS documents, that those documents be distributed to the relevant stakeholders, and that an updated REMS Patient Brochure be given out every time the patient receives a dose of Prolia®.[10]

II. ARGUMENT

Amgen has been vigilant in monitoring and evaluating the risk of MVF associated with the discontinuation of Prolia®. Amgen has proactively communicated the results of its safety assessments to FDA and collaborated with the Agency on updating the approved Prolia® labeling, including the Medication Guide, to accurately reflect the known risks of MVF.

The Prolia® labeling changes reflect the available information on the risk of MVF following treatment discontinuation, including current Agency and Amgen recommendations to mitigate this risk in clinical practice. FDA determined that the revised labeling in the Package Insert (Sections 5.6, Warnings and Precautions; 6.1, Adverse Reactions; and 17, Patient Counseling Information) and the Medication Guide appropriately inform healthcare practitioners and patients about this risk to ensure that the benefits of Prolia® treatment continue to outweigh its risks, including when treatment is stopped, for all of its approved indications. Importantly, neither FDA nor Amgen concluded that the risk of MVF associated with discontinuation of Prolia® treatment would be better communicated through a Boxed Warning or modification of the Prolia® REMS. Further, based on the totality of available data on the risk of MVF following Prolia® treatment discontinuation, the evidence does not meet the statutory and regulatory criteria for a Boxed Warning or modifications to the current REMS.

The current Package Insert and Medication Guide inform both healthcare practitioners and patients regarding the risk of MVF following treatment discontinuation. Among other things, the Package Insert features a warning as well as a description of the risk of MVF following denosumab discontinuation reported in Prolia® clinical trials, including risk factors for MVF (*i.e.*, that prior vertebral fracture is a predictor of multiple vertebral fractures after discontinuation). Finally, both the Package Insert and Medication Guide highlight the importance of patients not discontinuing Prolia® treatment without a discussion with their prescribing physician, and emphasize that if Prolia® treatment is discontinued, alternative antiresorptive therapy should be considered. Consistent with FDA regulations, the Medication Guide is available for distribution to patients with every dose of Prolia® administered by a healthcare practitioner.

Moreover, the literature and cases cited by the Petitioner have been reviewed and assessed through Amgen's standard pharmacovigilance review activities and communications with health authorities, including FDA. In fact, the information provided by the Petitioner

[10] *Id.*

formed part of Amgen's and the FDA's decision to update the Prolia® labeling in January 2017, which resulted in the labeling changes described above. Amgen believes that these labeling changes thoroughly communicate the appropriate information to help practitioners and patients mitigate the possibility of the MVF risk. Furthermore, since the time of these labeling changes, no new material information has come to light or been presented – including the more recent sources cited by the Petitioner – that would change the benefit/risk profile of Prolia®, as currently labeled, in its approved indications.

A. The Current FDA-Approved Package Insert and Medication Guide for Prolia® Thoroughly Inform Healthcare Practitioners

Amgen is committed to timely, appropriate, and transparent communication of risks related to its products to patients, healthcare professionals, and regulatory agencies. For marketed products like Prolia®, the risks are communicated to prescribing physicians and other healthcare professionals through product labeling, and to patients through updates to the product label, as well as patient-directed communications, such as the Medication Guide, as needed. Importantly, FDA has the final authority on the most appropriate way to communicate safety risk information to ensure that a product's benefits continue to outweigh its risks.

Amgen has worked collaboratively with FDA to update the Prolia® labeling with appropriate risk information directed to healthcare practitioners and patients regarding all known safety risks associated with use of Prolia®, including the potential risk of MVF following discontinuation of treatment. To address this risk, Amgen submitted a prior approval supplement in July 2016 to propose changes to the Prolia® labeling. FDA approved that supplement in January 2017 to incorporate relevant information in the Warnings and Precautions Section (5.6), Adverse Reactions Section (6.1 and 6.2), Patient Counseling Information Section (17), and in the Prolia® Medication Guide.[11] These changes to the approved labeling represent the Agency's determination, and Amgen's concurrence, that communicating such information to patients and to healthcare practitioners in the Package Insert and Medication Guide appropriately ensures a favorable benefit/risk profile for Prolia®.

[11] *See* Approval Letter, BLA 125320/S-180 (January 31, 2017), *available at* https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2017/125320Orig1s180ltr.pdf.

1. The Current Prolia® Package Insert Clearly Informs Healthcare Practitioners Regarding the Risk of MVF Following Treatment Discontinuation

The Prolia® labeling currently includes the following information in the Warnings and Precautions section:

> **5.6 Multiple Vertebral Fractures (MVF) Following Discontinuation of Prolia Treatment**
>
> Following discontinuation of Prolia treatment, fracture risk increases, including the risk of multiple vertebral fractures. Cessation of Prolia treatment results in markers of bone resorption increasing above pretreatment values then returning to pretreatment values 24 months after the last dose of Prolia. In addition, bone mineral density returns to pretreatment values within 18 months after the last injection [see Pharmacodynamics (12.2), Clinical Studies (14.1)].
>
> New vertebral fractures occurred as early as 7 months (on average 19 months) after the last dose of Prolia. Prior vertebral fracture was a predictor of multiple vertebral fractures after Prolia discontinuation. Evaluate an individual's benefit-risk before initiating treatment with Prolia.
>
> If Prolia treatment is discontinued, consider transitioning to an alternative antiresorptive therapy [see Adverse Reactions (6.1)].[12]

Additionally, the Adverse Reactions section includes a detailed description of MVF adverse events reported in the osteoporosis clinical trial program.[13] Specifically, this section describes the incidence of new vertebral fractures and MVF in the Phase 3 trial in women with postmenopausal osteoporosis.[14] Information regarding the mean time to onset (17 months) and the range (7 to 43 months) has also been included here.[15] Finally, this section notes that "prior vertebral fracture was a predictor" of MVF after discontinuation.[16]

Since the initial approval of Prolia® in 2010, the Dosage and Administration and Patient Counseling sections of the Package Insert have also advised prescribers that "[i]f a dose of Prolia

[12] Package Insert (July 26, 2019) at 5.6.

[13] *Id.* at 6.1. Section 6.2 also identifies MVF as a serious adverse event.

[14] *Id.*

[15] *Id.*

[16] *Id.*

is missed, administer the injection as soon as the patient is available."[17] Finally, since the time of initial approval in 2010, the Pharmacodynamics and Clinical Studies sections of the Package Insert have also informed healthcare practitioners regarding the reversibility of the effect of denosumab on markers of bone resorption.[18]

2. The Current Prolia® Medication Guide Provides Patients with Essential Information Regarding the Risk of MVF Following Treatment Discontinuation

FDA may require preparation and distribution of a Medication Guide if the Agency determines that "it is necessary to patients' safe and effective use of drug products."[19] In particular, FDA may require a drug product to be distributed with a Medication Guide in any of the following circumstances:

- "patient labeling could help prevent serious adverse effects";
- "information concerning a serious risk could affect patients' decision to use, or to continue to use" the drug product; or
- "patient adherence to directions for use is crucial to the drug's effectiveness."[20]

Because they are designed to provide key information directly to patients, Medication Guides must be consistent with the approved Package Insert but written in "nontechnical, understandable language."[21]

Consistent with these regulations, FDA approved Amgen's labeling supplement in 2017 to revise the Medication Guide to provide information directly to patients in succinct, nontechnical language. The Medication Guide now includes the following information for patients:

- **Increased risk of broken bones, including broken bones in the spine, after stopping Prolia.** After your treatment with Prolia is stopped, your risk for breaking bones, including bones in your spine, is increased. Your risk for having more than 1 broken bone in your spine is increased if you have already had a broken bone in your spine. Do not stop taking Prolia without first

[17] *Id.* at 2.2, 17.10.

[18] *Id.* at 12.2 ("After discontinuation of Prolia therapy, markers of bone resorption increased to levels 40-60% above pretreatment values but returned to baseline levels within 12 months.")

[19] 21 CFR 208.1(b).

[20] 21 CFR 208.1(c).

[21] 21 CFR 208.20(a).

> talking with your doctor. If your Prolia treatment is stopped, talk to your doctor about other medicine that you can take.[22]

The Medication Guide also instructs patients that "If you miss a dose of Prolia, you should receive your injection as soon as you can."[23]

The Medication Guide is available for distribution with each unit dose package of Prolia® and is also available on the Prolia® website.[24] Healthcare practitioners are instructed to provide the Medication Guide every time a patient is administered Prolia®.

3. The Current Prolia® Package Insert and Medication Guide Comprehensively Inform Healthcare Practitioners and Patients Regarding the Risk of MVF Following Treatment Discontinuation

Taken together, the existing Package Insert and Medication Guide comprehensively describe for both patients and healthcare practitioners the known risk of MVF following discontinuation of Prolia® treatment. The Package Insert clearly informs healthcare practitioners of the existence of the risk as well as the known incidence of the risk in relevant clinical trials. Healthcare practitioners are also informed of appropriate measures to mitigate the risk by (1) evaluating an individual's benefit-risk before initiating treatment with Prolia®; (2) advising patients not to interrupt Prolia® therapy; and (3) considering whether patients should be transitioned to an alternative antiresorptive therapy following discontinuation. Finally, the Medication Guide clearly informs patients regarding the "increased risk of broken bones, including broken bones in the spine" and advises patients not to discontinue Prolia® without first discussing with their doctor.

B. A Boxed Warning is not Necessary Because the Current Labeling, including the Package Insert and Medication Guide, Adequately Informs Healthcare Practitioners and Patients Regarding the Risk of MVF Following Discontinuation of Prolia®

FDA requires that serious or otherwise clinically significant adverse reactions and potential safety hazards be described in the Warnings and Precautions section of a drug product's Package Insert.[25] Information in this section must include, *inter alia*, a "succinct description of

---

[22] Package Insert (July 26, 2019) at Medication Guide.

[23] *Id.*

[24] *See* www.prolia.com.

[25] 21 CFR 201.57(c)(6); s*ee also Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format* (October 2011) ("*Labeling Guidance*") at 3-5.

the adverse reaction and outcome," key risk factors, and mitigation steps that may help to "decrease the likelihood, shorten the duration, or minimize the severity of an adverse reaction."[26]

FDA may require certain contraindications or serious warnings to be presented in a Boxed Warning on the labeling, particularly if the condition prompting the warning may lead to death or serious injury. Not every safety risk described in a Warning, Precaution or Contraindication should be included in a Boxed Warning. Instead, FDA has described a Boxed Warning as its "strongest" and "most prominent" warning," indicating its use for only the most serious adverse reactions that cannot be appropriately addressed *via* other labeling.[27]

The Petition requests FDA to find that "a more prominent Boxed Warning is needed to strengthen the current warnings found in the FDA-approved labeling of Prolia."[28] Agency guidance documents identify three situations in which FDA may require a drug product's labeling to carry a Boxed Warning. First, FDA will use a Boxed Warning when "[t]here is an adverse reaction so serious in proportion to the potential benefit from the drug (e.g., fatal, life-threatening or permanently disabling adverse reaction) that it is essential that it be considered in assessing the risks and benefits of using the drug"[29] FDA will also include a Boxed Warning when "[t]here is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug (e.g., patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug or managing patients in a specific manner, avoiding use in a specific clinical situation)."[30] Finally, Boxed Warnings are used when a drug has been approved with restrictions to assure safe use under "subpart H" or Elements To Assure Safe Use under a REMS.[31] None of these criteria applies to Prolia®.

Amgen's overall assessment of the clinical and post-marketing data supports that the risk of MVF warranted inclusion in the Warnings and Precautions section of the Package Insert and an addition to the Medication Guide, due to being a clinically significant adverse reaction as defined in the Agency guidance documents. Amgen's assessment was confirmed through FDA's

---

[26] *Id*. at 6.

[27] *See, e.g.*, FDA Drug Safety Communication, FDA warns about rare but serious risks of stroke and blood vessel wall tears with multiple sclerosis drug Lemtrada (alemtuzumab) (November 29, 2018), *available at* https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-rare-serious-risks-stroke-and-blood-vessel-wall-tears-multiple-sclerosis-drug; FDA Drug Safety Communication, FDA adds Boxed Warning for increased risk of death with gout medicine Uloric (febuxostat) (February 21, 2019), *available at* https://www.fda.gov/drugs/drug-safety-and-availability/fda-adds-boxed-warning-increased-risk-death-gout-medicine-uloric-febuxostat.

[28] Petition at 16.

[29] 21 CFR 201.57(c)(1); s*ee also Labeling Guidance* at 11-12.

[30] *Labeling Guidance* at 11-12.

[31] *Id*.

approval of the January 2017 labeling changes. There has been no change to the benefit/risk profile of Prolia® since January 2017, and no new information has become available to alter the conclusion that the MVF risk is appropriately addressed by the FDA-approved Package Insert and Medication Guide. Thus, the current Prolia® labeling is consistent with FDA's labeling regulations and guidance, and a Boxed Warning is neither appropriate nor necessary.

C. Amgen's Distribution of the Revised Medication Guide to Patients Adequately Addresses the Petitioner's Request that Amgen Revise the REMS Documents and Ensure that a Patient Brochure is Provided to Patients with Each Administered Dose of Prolia®

Prolia® was approved with a REMS to ensure that the benefits of Prolia® outweigh its risks. The REMS consists of a Medication Guide, a communication plan and a timeline of assessments.[32] The Petition requests that FDA require that Amgen update the REMS documents to include additional information regarding the risk of MVF following treatment discontinuation. The Petition also requests that FDA require that Amgen update the REMS Patient Brochure and ensure that the Patient Brochure be given to patients with each dose administered.[33] Amgen believes that the 2017 revisions to the Medication Guide, which is to be provided to patients every time Prolia® is administered, adequately communicates the risk of MVF following discontinuation of Prolia® treatment.

It is Amgen's position that the benefit/risk profile of Prolia® as labeled remains favorable in its approved indications, given the data available to date regarding the risk of MVF after treatment discontinuation. The current FDA-approved labeling reflects the most appropriate means of addressing the risk of MVF following discontinuation of Prolia®. Over-warning can have unintended consequences, including discouraging appropriate treatment. Prolia® is indicated for patients with osteoporosis at high risk of fracture, a condition associated with high levels of mortality and morbidity and recognized as undertreated.[34] Adding an additional risk to the current REMS could also have the unintentional effect of diluting risk communication within the Prolia® REMS, given that the current Prolia® REMS already contains five adverse events of special interest (hypocalcemia, osteonecrosis of the jaw, atypical femoral fracture, serious infection including skin infection and dermatologic adverse events).

---

[32] *Id*. *See* Approval Letter, BLA 125320 (June 1, 2010) at 22, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/125320s000Approv.pdf

[33] Petition at 2.

[34] *See, e.g.*, S. Khosla and E. Shane, A Crisis in the Treatment of Osteoporosis, Journal of Bone and Mineral Research (June 22, 2016), *available at* https://onlinelibrary.wiley.com/doi/abs/10.1002/jbmr.2888.

In January 2017, FDA and Amgen determined that a statement regarding the risk of MVF following discontinuation of Prolia® should be included in the Medication Guide, which is part of the Prolia® REMS.[35] As previously described, the Medication Guide now includes the following information directed to patients:

- **Increased risk of broken bones, including broken bones in the spine, after stopping Prolia**. After your treatment with Prolia is stopped, your risk for breaking bones, including bones in your spine, is increased. Your risk for having more than 1 broken bone in your spine is increased if you have already had a broken bone in your spine. Do not stop taking Prolia without first talking with your doctor. If your Prolia treatment is stopped, talk to your doctor about other medicine that you can take.[36]

However, the Agency and Amgen did not conclude that the REMS materials should be modified to include the risk of MVF following discontinuation. This reflects the determination that a modification of the REMS is not necessary to ensure that the benefit of Prolia® outweighs the risk of MVF following treatment discontinuation.

Consistent with FDA regulations and with the Prolia® REMS, Amgen has ensured that the revised Medication Guide is available with each single use package for healthcare practitioners to provide every time a patient is administered Prolia®.[37] The carton and container package also include an instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed.[38] Amgen also makes the revised Medication Guide accessible on the Prolia® patient website, and it is also available online at FDA's Medication Guide Database.[39]

The Petition contains no new material information that was unavailable to FDA at the time the Agency concluded that distribution of a revised Medication Guide was sufficient to properly inform patients regarding the risk of MVF following treatment discontinuation. Nor does the Petition provide any evidence that distribution of the revised Medication Guide fails to sufficiently inform patients of the importance of not missing a scheduled dose of Prolia®. For

---

[35] Should FDA ever determine that a REMS is no longer needed for Prolia®, the Medication Guide would remain as part of the Prolia® labeling.

[36] Package Insert (July 26, 2019) at Medication Guide.

[37] *See* Risk Assessment and Risk Mitigation Review (May 19, 2010) at 8, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/125320s000RiskR.pdf.

[38] *Id.*

[39] *See* FDA, Medication Guides, *available at* https://www.fda.gov/drugs/drug-safety-and-availability/medication-guides.

these reasons, Amgen respectfully requests that FDA deny the Petitioner's request to require updating of the REMS documents, including the Patient Brochure.

IV. CONCLUSION

For the reasons described above, Amgen urges FDA to deny the Petitioner's requests that (1) FDA require a Boxed Warning regarding MVF risks to the labeling for Prolia®, and (2) modify the Prolia® REMS. The Petitioner has not provided any new evidence that the existing Package Insert and Medication Guide do not sufficiently inform patients and healthcare practitioners regarding the risk of MVF associated with discontinuation of Prolia®.

As with all of the products it markets, Amgen will continue to monitor the safety of Prolia® and remains committed to working with the Agency to ensure patient safety by addressing any new data as they may arise.

Sincerely,

Lynn Mehler
Hogan Lovells US LLP
555 13th Street, NW
Washington, DC 20004
202-637-6419
lynn.mehler@hoganlovells.com

Cc: Hylton V. Joffe, M.D., M.M.Sc.
Director, Division of Bone, Reproductive and Urologic Products
Center for Drug Evaluation and Research
Food and Drug Administration

Carol J. Bennett, J.D.
Deputy Director, Office of Regulatory Policy
Center for Drug Evaluation and Research
Food and Drug Administration