Meena Aladdin, M.S., Ph.D
Michael A. Carome, M.D.
Sidney M. Wolfe, M.D.
Public Citizen's Health Research Group
1600 20th Street, NW
Washington, D.C. 20009

Re: Docket No. FDA-2019-P-1818

4/23/2020

Dear Dr. Aladdin, Dr. Carome, and Dr. Wolfe:

This letter responds to your citizen petition received on April 16, 2019 (Petition) requesting that the Food and Drug Administration (FDA or Agency) require: (1) the addition of a boxed warning to the Prolia (denosumab) product labeling describing the risk of vertebral fractures upon drug discontinuation (Petition at 1, 17); and (2) implementation of an updated Risk Evaluation and Mitigation Strategy (REMS) that highlights the risk of multiple vertebral fractures following discontinuation of Prolia treatment and that describes steps that can be taken to mitigate this risk (Petition at 2, 17-18).

We have carefully considered the issues raised in your Petition and the comments submitted by Amgen, Inc. (Amgen). For the reasons stated below, your Petition is denied. However, as described more fully below, today FDA is approving certain changes to Prolia's labeling to clarify the information regarding the risk of multiple vertebral fractures upon drug discontinuation.

I. BACKGROUND

A. Prolia—Labeling and REMS

On June 1, 2010, FDA approved the biologics license application (BLA) 125320 for Prolia (denosumab), submitted by Amgen.[1] Prolia is an injection for subcutaneous use, indicated for the treatment of postmenopausal women with osteoporosis with high risk for fracture. The WARNINGS AND PRECAUTIONS section of the Prolia labeling and the Medication Guide currently contain a warning about the risk of multiple vertebral fractures following the discontinuation of the drug. Since approval of Prolia, the WARNINGS AND PRECAUTIONS section of the product labeling has contained the following statement on bone suppression:

> **5.10 Suppression of Bone Turnover**
>
> In clinical trials in women with postmenopausal osteoporosis, treatment with Prolia resulted in significant suppression of bone remodeling as evidenced by markers of bone turnover and bone histomorphometry *[see Clinical Pharmacology (12.2), Clinical Studies (14.1)]*. The significance of these findings and the effect of long-term treatment with Prolia are unknown. The long-term consequences of the degree of suppression of bone remodeling observed with Prolia may contribute to adverse outcomes such as osteonecrosis of the jaw, atypical fractures, and delayed fracture healing. Monitor patients for these consequences.

The reversal of bone turnover and bone mineral density has also been described in product labeling since initial approval (specific language is underlined):

[1] The BLA 125320 encompasses both Prolia (osteoporosis indications and currently with a REMS) and Xgeva (oncology indications and does not currently have a REMS). The Petition and this response pertain only to Prolia.

12.2 Pharmacodynamics

In clinical studies, treatment with 60 mg of Prolia resulted in reduction in the bone resorption marker serum type 1 C-telopeptide (CTX) by approximately 85% by 3 days, with maximal reductions occurring by 1 month. CTX levels were below the limit of assay quantitation (0.049 ng/mL) in 39% to 68% of subjects 1 to 3 months after dosing of Prolia. At the end of each dosing interval, CTX reductions were partially attenuated from a maximal reduction of ≥ 87% to ≥ 45% (range: 45% to 80%), as serum denosumab levels diminished, reflecting the reversibility of the effects of Prolia on bone remodeling. These effects were sustained with continued treatment. Upon reinitiation, the degree of inhibition of CTX by Prolia was similar to that observed in patients initiating Prolia treatment.

Consistent with the physiological coupling of bone formation and resorption in skeletal remodeling, subsequent reductions in bone formation markers (i.e., osteocalcin and procollagen type 1 N-terminal peptide [PlNP]) were observed starting 1 month after the first dose of Prolia. After discontinuation of Prolia therapy, markers of bone resorption increased to levels 40% to 60% above pretreatment values but returned to baseline levels within 12 months.

14.1 Postmenopausal Women with Osteoporosis

Effect on Bone Mineral Density (BMD)
Treatment with Prolia significantly increased BMD at all anatomic sites measured at 3 years. The treatment differences in BMD at 3 years were 8.8% at the lumbar spine, 6.4% at the total hip, and 5.2% at the femoral neck. Consistent effects on BMD were observed at the lumbar spine, regardless of baseline age, race, weight/body mass index (BMI), baseline BMD, and level of bone turnover.

After Prolia discontinuation, BMD returned to approximately baseline levels within 12 months.

In addition, in January 2017, following a clinical review by FDA, the Agency agreed with Amgen's proposal to add information concerning post-discontinuation vertebral fractures to the Prolia labeling, including a warning and precaution because of the potential for serious, irreversible disability, and the likelihood that prescriber awareness would avert some of these events (2017 Supplement). The ADVERSE REACTIONS section of the labeling was also modified in 2017 to address the risk of multiple vertebral fractures. The new language regarding vertebral fractures added to the WARNINGS AND PRECAUTIONS section is as follows:

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)]*.

The January 2017 Supplement language regarding vertebral fractures in the ADVERSE REACTIONS section is as follows:

6.1 Clinical Trials Experience

Multiple Vertebral Fractures (MVF) Following Discontinuation of Prolia Treatment
In the osteoporosis clinical trial program, multiple vertebral fractures were reported in patients after discontinuation of Prolia. In the phase 3 trial in women with postmenopausal osteoporosis, 6% of women who discontinued Prolia and remained in the study developed new vertebral fractures, and 3% of women who discontinued Prolia and remained in the study developed multiple new vertebral fractures. The mean time to onset of multiple vertebral fractures was 17 months (range: 7-43 months) after the last injection of Prolia. Prior fracture was a predictor of multiple vertebral fractures after discontinuation *[see Warnings and Precautions (5.6)]*.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of Prolia:

- Drug-related hypersensitivity reactions: anaphylaxis, rash, urticaria, facial swelling, and erythema
- Hypocalcemia: severe symptomatic hypocalcemia
- Musculoskeletal pain, including severe cases
- Parathyroid Hormone (PTH): Marked elevation in serum PTH in patients with severe renal impairment (creatinine clearance < 30 mL/min) or receiving dialysis
- Multiple vertebral fractures following discontinuation of Prolia

Similar language regarding multiple vertebral fractures can also be found in the **PATIENT COUNSELING INFORMATION** section and the MEDICATION GUIDE.

Multiple Vertebral Fractures (MVF) Following Discontinuation of Prolia Treatment

Advise patients not to interrupt Prolia therapy without talking to their physician *[see Warnings and Precautions (5.6)]*.

Medication Guide

- **Increased risk of broken bones, including broken bones in the spine, after stopping Prolia.**
  Talk to your doctor before starting Prolia treatment. After your treatment with Prolia is stopped, or if you skip or delay taking a dose, 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 broken a bone in your spine. Do not stop, skip, or delay 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.

In a supplement approved on October 1, 2019, this language was modified to add clarifying information for patients as follows: "Increased risk of broken bones, including broken bones in the spine, after stopping, skipping or delaying Prolia."

The REMS for Prolia was implemented at the time of the approval of the drug product in 2010. The goal of the PROLIA REMS is to mitigate the risks of hypocalcemia, osteonecrosis of the jaw, atypical femoral fractures, serious infections, and dermatologic reactions by:

1. [I]nforming healthcare providers and patients about the risks of (1) hypocalcemia, (2) osteonecrosis of the jaw, (3) atypical femoral fractures, (4) serious infections, and (5) dermatologic reactions associated with PROLIA

2. [I]nforming healthcare providers to counsel patients about the risks associated with PROLIA.

As described above, the Prolia labeling and REMS provide information and warnings on the risk of multiple vertebral fractures upon discontinuation of use. The REMS for Prolia includes a Medication Guide and a Dear Health Care provider letter. The Prolia REMS has been modified on multiple occasions to address the risk of hypocalcemia, atypical femoral fractures, and

osteonecrosis of the jaw. As part of the REMS, the healthcare provider should discuss the risks and symptoms of each risk with the patient. The healthcare provider should also provide a copy of the Medication Guide to each patient.

B. Drug Labeling and REMS Regulatory Framework

1. Warnings and Precautions and Boxed Warnings

Proposed drug product labeling must be submitted with all new drug applications.[2] Labeling for prescription drug products is generally governed by 21 CFR 201.50, *et seq*., with specific requirements for content and format set forth in 21 CFR 201.57. FDA regulations state that the WARNINGS AND PRECAUTIONS section of prescription drug labeling (including the product's package insert) must describe clinically significant adverse reactions, other potential safety hazards, limitations on use imposed by them, and steps that should be taken if these situations occur (21 CFR 201.57(c)(6)(i); see also 21 CFR 201.80(e) and (f)). Further, "the labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitively established." 21 CFR 201.57(c)(6). FDA's guidance for industry *Warnings and Precautions, Contraindications, and Boxed Warnings Sections of Labeling for Human Prescription Drug and Biological Products—Content and Format* (Warnings and Precautions Guidance) describes some factors that FDA may consider in assessing whether there is reasonable evidence of a causal relationship. These include:

> (1) [T]he frequency of reporting; (2) whether the adverse event rate in the drug treatment group exceeds the rate in the placebo and active-control group in controlled trials; (3) evidence of a dose-response relationship; (4) the extent to which the adverse event is consistent with the pharmacology of the drug; (5) the temporal association between drug administration and the event; (6) the existence of dechallenge and rechallenge experience; and (7) whether the adverse event is known to be caused by related drugs.[3]

Under § 201.57(c)(1), a boxed warning may be required for certain contraindications or serious warnings, particularly those that may lead to death or serious injury (see also § 201.80(e)). A boxed warning must contain, in uppercase letters, a heading that includes the word "WARNING" and other words that convey the general focus of information in the box. A boxed warning briefly explains the risk and refers to more detailed information in the CONTRAINDICATIONS or WARNINGS AND PRECAUTIONS section (§ 201.57(c)(1)). A summary of a boxed warning (with the heading WARNING and other words identifying the subject of the warning) must be included in the HIGHLIGHTS section in a box and in bold type (§§ 201.56(d)(1) and 201.57(a)(4)).

FDA's Warnings and Precautions Guidance states that a boxed warning ordinarily is used to highlight one of the following situations:

- There is an adverse reaction so serious in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening or permanently disabling adverse reaction) that it is essential that it be considered in assessing the risks and benefits of using a drug

  OR

- There 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)

  OR

[2] 21 U.S.C. 355(b)(1)(F); 21 CFR 314.50.

[3] See FDA's guidance for industry *Warnings and Precautions, Contraindications, and Boxed Warnings Sections of Labeling for Human Prescription Drug and Biological Products—Content and Format* (October 2011), available at https://www.fda.gov/media/71866/download. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs.

- FDA approved the drug with restrictions to ensure safe use because FDA concluded that the drug can be safely used only if its distribution or use is restricted (e.g., under 21 CFR 314.520 and 601.42 "Approval with restrictions to assure safe use" or under 505-1(f)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) "Risk Evaluation and Mitigation Strategies" Elements to assure safe use).[4]

The Warnings and Precautions Guidance also states that there may be other situations in which a boxed warning may be appropriate to highlight information that is especially important to a prescriber.[5]

Section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)[6] authorizes FDA to require holders of approved applications for prescription drug products to certain labeling changes—including requiring or modifying a boxed warning—based on "new safety information.". New safety information is defined in part as:

> Information derived from a clinical trial, an adverse event report, a post approval study (including a study under section 505(o)(3) [of the FD&C Act]), or peer-reviewed biomedical literature; data derived from the postmarket risk identification and analysis system under section 505(k) [of the FD&C Act]; or other scientific data deemed appropriate by the [Agency] about [among other things] a serious risk or an unexpected serious risk associated with use of the drug that the [Agency] has become aware of (that may be based on a new analysis of existing information) since the drug was approved, since [a] risk evaluation and mitigation strategy (REMS) [for the drug] was required, or since the last assessment of the approved [REMS].[7]

2. REMS

The Food and Drug Administration Amendments Act of 2007[8] created section 505-1 of the FD&C Act, which authorizes FDA to require a REMS if FDA determines that a REMS is necessary to ensure that the benefits of the drug outweigh its risks.[9] A REMS is a required risk management strategy that employs tools beyond prescribing information to ensure that the benefits of a drug outweigh its risks. A REMS may require a Medication Guide (or patient package insert) to provide risk information to patients[10] and/or a communication plan to disseminate risk information to health care providers.[11] FDA may also require certain Elements to Assure Safe Use (ETASU) when such elements are necessary to mitigate specific serious risks associated with a drug.[12] The ETASU may include, for example, requirements that health care providers who prescribe the drug have particular training or experience, that patients using the drug be monitored, or that the drug be dispensed to patients with evidence or other documentation of safe-use conditions.

Certain REMS with ETASU may also include an implementation system through which the applicant is able to monitor and evaluate implementation of the ETASU and work to improve their implementation.[13] Finally, REMS generally must have a timetable for submission of assessments of the strategy.[14] FDA can require a REMS before initial approval of a new drug application (NDA) and BLA or, should FDA become aware of new safety information[15] about a drug and determine that a REMS is necessary to ensure that the benefits of the drug outweigh its risks, after the drug has been approved.[16] When FDA determines that a modification of a REMS is necessary to ensure that the benefits of a drug outweigh its risks or to minimize

[4] Warnings and Precautions Guidance at 11.
[5] Warnings and Precautions Guidance at 11–12.
[6] See also the July 2013 guidance for industry *Safety Labeling Changes—Implementation of Section 505(o)(4) of the FD&C Act*, available at https://www.fda.gov/media/116594/download.
[7] See section 505-1(b)(3) of the FD&C Act (21 U.S.C. 355-1(b)(3)).
[8] Public Law 110-85.
[9] Section 505-1(a) of the FD&C Act.
[10] Section 505-1(e)(2) of the FD&C Act.
[11] Section 505-1(e)(3) of the FD&C Act.
[12] Section 505-l(f)(3) of the FD&C Act.
[13] Section 505-1(f)(4) of the FD&C Act.
[14] Section 505-1(d) of the FD&C Act.
[15] Section 505-1(b)(3) of the FD&C Act.
[16] Section 505-1(a) of the FD&C Act.

the burden on the health care delivery system of complying with the REMS, FDA has authority to require that the application holder submit a proposed modification to a REMS under section 505-1(g) of the FD&C Act.[17]

II. DISCUSSION

A. Boxed Warning

Your Petition requests that FDA require the addition of a boxed warning to the Prolia labeling describing the risk of vertebral fractures upon discontinuation of the drug product (Petition at 1, 17). You suggest the following language, which is adapted from the current WARNINGS AND PRECAUTIONS regarding Multiple Vertebral Fractures Following Discontinuation of Prolia Treatment, for the requested boxed warning, and recommends that conforming changes be made to other sections of the product labeling:

> WARNING: MULTIPLE VERTEBRAL FRACTURES FOLLOWING DISCONTINUATION OF PROLIA TREATMENT
>
> Following discontinuation of Prolia treatment, the risk of vertebral fractures, including the risk of multiple vertebral fractures, rapidly increases. 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) and 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 profile before initiating treatment with Prolia. Data from case series strongly suggests that vertebroplasty is not an effective treatment for vertebral fractures that occur following cessation of denosumab treatment and can cause additional vertebral fractures.
>
> If Prolia treatment is discontinued, the patient should promptly receive a bisphosphonate or other alternative antiresorptive therapy to mitigate the increased risk of vertebral fracture [see *Adverse Reactions* (6.1)].

The WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS sections of the Prolia professional labeling and the Medication Guide currently contain a warning about the risk of multiple vertebral fractures following the discontinuation of the drug. You request that FDA require Amgen to make this warning more prominent in the labeling by moving it to a boxed warning and modifying the content of the warning (Petition at 1-2, 5-6). You provide data and information from clinical trials, observational studies, and case series describing the rapid reversal of Prolia's positive effects and an increased risk of vertebral fractures upon cessation of treatment (Petition at 8-16). You assert that the nature of multiple, often preventable vertebral fractures, accompanied by potentially severe pain and disability, is such that a more prominent boxed warning is needed to strengthen the current warnings found in the FDA-approved labeling of Prolia (Petition at 16). You contend that a boxed warning is warranted because the risk of multiple vertebral fractures following cessation of denosumab can either be avoided by not stopping denosumab unnecessarily or be mitigated by immediately transitioning patients to another antiresorptive therapy, such as a bisphosphonate, after cessation of denosumab treatment (Petition at 16).

In the review of the Prolia BLA and the 2017 Supplement, FDA considered that treatment with Prolia for osteoporosis results in substantial decreased risk of fractures (vertebral, nonvertebral and hip fracture). Furthermore, we also understood the importance of the fact that the intended patient population for Prolia is women at high risk for fracture, and Prolia may be used in women with severe renal impairment, unlike some other osteoporosis drug products. The labeling changes approved in the January 2017 Supplement relate to the potential increased fracture risk once the drug is stopped, which is the same concern outlined in your Petition. Currently, there are six classes of products approved for osteoporosis (calcitonin, bisphosphonates, parathyroid hormone-related products, RANK-ligand inhibitors, estrogen agonist/antagonists, and sclerostin inhibitors).

[17] See Risk Evaluation and Mitigation Strategies: Modifications and Revisions Guidance for Industry (July 2019).

Bisphosphonates are unique in that they are retained in bone and cessation of therapy does not result in the immediate reversal of the bone gain achieved. For all other classes of approved products, cessation of therapy results in reversal of the bone gain achieved. As bone density decreases after therapy is stopped, the risk of fracture increases.

Much of the data provided in your Petition was reviewed and considered by FDA at the time of Amgen's 2017 Supplement when the WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS sections of the labeling were updated to include the risk of multiple vertebral fractures following discontinuation of treatment. In fact, some of the studies that you submitted provided crucial data and evidence to support the 2017 labeling changes. At that time, we did not find that the information from the studies rose to the level of requiring the Prolia labeling to carry a boxed warning.

In considering the actions requested in your Petition, we have reviewed all the studies and data discussed in your submission. Several of the studies you cite support the rapid reversal of bone turnover suppression and bone mineral density increases seen with cessation of Prolia.[18] You also provide data and information on patients with vertebral fractures following denosumab discontinuation.[19] The current WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS sections of the Prolia labeling describe and warn about bone turnover suppression and vertebral fractures following discontinuation of treatment of the drug product. In fact, the reversal of bone turnover and bone mineral density has been described in the product labeling since the approval of Prolia (see **12.2 Pharmacodynamics**). Several other studies discussed in your Petition focus on the mechanism of action of the bisphosphonate class of drugs and Prolia.[20] With respect to bisphosphonates, FDA agrees that the mechanisms of action of these products are different. While both products act to inhibit bone resorption, bisphosphonates are taken up into bone where they can reside for years. Prolia is not taken up into bone tissue and therefore would not have a long residence time or pharmacologic activity in the body.

In addition to reviewing the studies cited in your Petition, we searched FDA's Adverse Event Reporting System (FAERS) database to identify other data that may be relevant to the risk of vertebral fractures following discontinuation of Prolia treatment. However, given the voluntary nature of spontaneous reporting, inherent limitations of the FAERS data (e.g., missing baseline characteristics, clinical details, medical history) and high background rate of vertebral fractures, causal inferences could not be made. It is difficult to discern the role of Prolia discontinuation from the progression of the underlying disease state, individual lifestyle factors, and genetic predisposition for vertebral fractures from individual case reports.

As discussed in this response, many of the studies presented in the Petition had already been reviewed by FDA when the Prolia labeling was amended to add information on multiple vertebral fractures in the WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS sections. The risk of multiple vertebral fractures upon drug discontinuation is appropriately included in these sections.

Based on the information, data, and studies you provided and information available to the Agency, we do not believe there is evidence to support the addition of a boxed warning regarding multiple vertebral fractures upon discontinuation of use of Prolia. The benefits of Prolia are significant and the risk of fracture after drug discontinuation is a risk that exists for most drug classes indicated for osteoporosis (except for the bisphosphonates class of drugs) and is not unique to Prolia. Several sections of the Prolia labeling clearly inform prescribers and patients of the product's level of bone turnover suppression,

[18] Zanchetta, MB, J Boailchuck, F Massari, F Silveira, C Bogado, and JR Zanchetta, 2018, Significant Bone Loss After Stopping Long-Term Denosumab Treatment: A Post FREEDOM Study, Osteoporos Int. epub ahead of print October 3, 2017, doi: 10.1007/s00198-017-4242-6; McClung, MR, RB Wagman, PD Miller, A Wang, and EM Lewiecki, 2017, Observations Following Discontinuation of Long-Term Denosumab Therapy, Osteoporos Int, epub ahead of print January 31, 2017, doi: 10.1007/s00198-017-3919-1.

[19] Anastasilakis, AD, SA Polyzos, P Makras, B Aubry-Rozier, S Kaouri, and O Lamy, 2017, Clinical Features of 24 Patients With Rebound-Associated Vertebral Fractures After Denosumab Discontinuation: Systematic Review and Additional Cases, J Bone Miner Res, epub ahead of print March 13, 2017, doi: 10.1002/jbmr.3110; Cummings, SR, S Ferrari, R Eastell, N Gilchrist, JB Jensen, M McClung, C Roux, O Törring, I Valter, AT Wang, and JP Brown, 2018, Vertebral Fractures After Discontinuation of Denosumab: A Post Hoc Analysis of the Randomized Placebo-Controlled FREEDOM Trial and Its Extension, J Bone Miner Res, epub ahead of print November 22, 2017, doi: 10.1002/jbmr.3337.

[20] Drake, MT, BL Clarke, and S Khosla, 2008, Bisphosphonates: Mechanism of Action and Role in Clinical Practice, Mayo Clin Proc, 83(9):1032–1045; Hanley, DA, JD Adachi, and V Brown, 2012, Denosumab: Mechanism of Action and Clinical Outcomes, Int J Clin Pract, 66(12):1139–1146.

reversal of this suppression, and warn of vertebral fractures upon discontinuation of use. As a result, we are not granting your request to elevate such an expected occurrence to a boxed warning.

Although we are not granting your request for a boxed warning, the Agency has concluded that the labeling should be clarified to improve prescriber understanding of the risk of multiple vertebral fracture following Prolia discontinuation and strengthen the recommendation that prescribers transition patients to another resorptive agent upon discontinuation. As a result, today FDA is approving certain changes to Prolia's labeling to clarify the information regarding the risk of multiple vertebral fractures upon drug discontinuation (the new language is underlined and the deleted language is displayed as a strikethough):

Highlights, Warning and Precautions:

- Multiple vertebral fractures have been reported following Prolia discontinuation. ~~Consider transitioning~~ Patients should be transitioned to another antiresorptive agent if Prolia is discontinued (5.6)

Full Prescribing Information, Warnings and Precautions:

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. Treatment with Prolia results in significant suppression of bone turnover and cessation of Prolia treatment results in increased bone turnover ~~in markers of bone resorption increasing~~ above pretreatment values 9 months after the last dose of Prolia. Bone turnover then returns 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~~ patients should be transitioned to an alternative potent antiresorptive therapy [see Adverse Reactions (6.1)].

B. Modification of the Prolia REMS

The REMS for Prolia was implemented at the time of the approval of the drug product in 2010. The goal of the PROLIA REMS is to mitigate the risks of hypocalcemia, osteonecrosis of the jaw, atypical femoral fractures, serious infections, and dermatologic reactions. The REMS for Prolia includes a Medication Guide and a Communication Plan, which includes a REMS Letter for Healthcare Providers, REMS Letter for Professional Societies, Patient Counseling Chart for Healthcare Providers, and a Patient Brochure. As part of the REMS, the healthcare provider should discuss the risks and symptoms of each risk with the patient. The healthcare provider must also provide a copy of the Medication Guide to each patient.

In addition to the labeling changes, you also request that FDA require the modification of the Prolia REMS to include the preparation and distribution of updated versions of the REMS Letter for Healthcare Providers, REMS Letter for Professional Societies, Patient Counseling Chart for Healthcare Providers, and Patient Brochure that highlight the risk of multiple vertebral fractures following discontinuation of Prolia treatment. You also request that the Patient Brochure describe the steps that can be taken to mitigate this risk (Petition at 2, 17-18).[21] You ask that the modified REMS require that the Patient Brochure be given to patients every time they receive a dose of Prolia (Petition at 17). You state that the modified Patient Brochure should explicitly warn patients about the increased risk of multiple vertebral fractures if they miss their next scheduled dose in six months or discontinue treatment without receiving alternative antiresorptive therapy to mitigate this risk (Petition at 17-18). To support this request, you provide data and information from clinical trials, observational studies, and case series describing the rapid reversal of Prolia's positive effects and an increased risk of vertebral fractures upon cessation of treatment (Petition at 8-16).

[21] An application holder can propose a REMS modification at any time and FDA can require a modification if it is necessary to ensure that the benefits of the drug outweigh the risks or to minimize the burden on the healthcare delivery system of complying with the REMS. FD&C Act 505-1(g)(4).

The Prolia REMS has been modified on multiple occasions to address the risk of hypocalcemia, atypical femoral fractures, and osteonecrosis of the jaw. However, as discussed in section II.A. above, FDA has thoroughly reviewed the studies, data, and information you submitted in your Petition, and we have determined that the REMS modifications you have requested are not necessary to ensure the benefits of Prolia outweigh its risks. The Medication Guide, which is a part of the product labeling (and an element of this REMS), is provided to patients. It currently contains patient information on this risk of bone fractures,[22] and the information currently contained within does not require updating. Therefore, patients receive information on this risk.

Additionally, as outlined in section II.A, the analysis of the data at the time of the 2017 labeling updates did not warrant a modification to the REMS, and that analysis stands. Therefore, your requested action with respect to the REMS is denied.

III. CONCLUSION

For the reasons explained above, your Petition is denied. We are denying your request for the addition of a boxed warning and REMS modifications. However, we have approved other labeling changes to clarify the risk of multiple vertebral fractures. With those changes, the current Prolia labeling adequately describes the risk of vertebral fractures upon drug discontinuation in the WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS sections. As always, FDA will continue to monitor the safety data, including adverse event reports, for Prolia and all other drugs regulated by FDA.

Sincerely,

Douglas C. Throckmorton -S

Digitally signed by Douglas C. Throckmorton -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300121270, cn=Douglas C. Throckmorton -S
Date: 2020.04.21 17:08:46 -04'00'

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

[22] The Prolia Medication Guide contains the following language on bone fractures: "**Increased risk of broken bones, including broken bones in the spine, after stopping, skipping or delaying Prolia.** Talk with your doctor before starting Prolia treatment. After your treatment with Prolia is stopped, or if you skip or delay taking a dose, 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, skip or delay 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."