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Citizen Petition

Date: April 16, 2019

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

On behalf of Public Citizen, a consumer advocacy organization with more than 500,000 members and supporters nationwide, and Public Citizen's Health Research Group, the undersigned submit this petition under Section 352 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 352) and under Food and Drug Administration (FDA) regulations at 21 C.F.R. §§ 10.30 and 201.56 to request that the Commissioner of Food and Drugs immediately take the actions requested below regarding the product labeling and risk evaluation and mitigation strategy for the osteoporosis drug Prolia (denosumab).

There is a growing body of evidence showing that cessation of Prolia is associated with an increased risk of multiple vertebral fractures. The risk of this serious adverse effect could be mitigated with a prominent boxed warning and an updated risk evaluation and mitigation strategy (REMS) that together would increase physician and patient awareness about the risks associated with treatment cessation. It also would discourage abrupt cessation of treatment or introduction of drug holidays without adequate consideration of alternative antiresorptive treatment options to protect patients from vertebral fractures.

A. ACTIONS REQUESTED

Immediately require the following:

(1) The addition of a boxed warning to the product labeling of Prolia describing the risk of vertebral fractures upon drug discontinuation. We suggest the following wording for the requested boxed warning:

> **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)].***

Conforming changes also should be made in other sections of the product labeling.

(2) Implementation of an updated REMS for Prolia that includes 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 and that describe steps that can be taken to mitigate this risk. The updated REMS should require that the Patient Brochure be given to patients every time they receive a dose of Prolia. The updated 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.

B. STATEMENT OF GROUNDS

1. Legal Standard

The legal standards applicable to the actions requested in this petition are as follows:

The addition of a boxed warning to the product labeling of Prolia describing the risk of vertebral fractures upon discontinuation of the drug

The FDA may require a boxed warning in the product labeling for prescription drugs for "[c]ertain contraindications or serious warnings, particularly those that may lead to death or serious injury."[1] The agency advises that a boxed warning ordinarily is used for cases in which there is an adverse reaction so serious in proportion to the potential benefit from the drug that it

[1] 21 C.F.R. § 201.57(c)(1).

should be considered in assessing the risks and benefits of using the drug or there is a serious adverse reaction that can be prevented or reduced in severity by appropriate use of the drug.[2]

The FDA has stated that in order to include an adverse reaction as a warning in the product labeling, "there should be reasonable evidence of a causal association between the drug and the adverse event, but a causal relationship need not have been definitively established."[3] In order to include such a warning as a boxed warning, evidence "ordinarily must be based on clinical data."[4]

In assessing evidence of a causal relationship for inclusion in the warnings section of a drug label, the FDA advises that factors to consider include "1) the 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 the drug administration and the event; 6) existence of dechallenge and rechallenge experience; and 7) whether the adverse event is known to be caused by related drugs."[5] Importantly, supporting evidence related to all of these factors is not necessary to establish reasonable evidence of a causal association between an adverse event and the use of a particular drug.

Update the REMS for Prolia to include distribution of an updated REMS Letter for Healthcare Providers that describes the increased risk of vertebral fractures upon drug discontinuation

The FDA may require a REMS after approval of a drug if the FDA becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the drug's benefits outweigh its risks.[6]

The FDA also may require modification of an existing approved REMS when the agency determines that such modification is necessary to ensure that the drug's benefits outweigh its risks.[7]

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[2] Food and Drug Administration. 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. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075096.pdf. Accessed April 10, 2019.

[3] *Ibid*.

[4] 21 C.F.R. § 201.57(c)(1).

[5] Food and Drug Administration. 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. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075096.pdf. Accessed April 10, 2019.

[6] 21 U.S.C. § 355-1(a)(2)(A).

[7] 21 U.S.C. § 355-1(g)(4)(B).

2. Regulatory Background on Prolia

Approved indications

Prolia was initially approved by the FDA in 2010 for treatment of postmenopausal women with osteoporosis at high risk for fracture.[8] The FDA subsequently approved Prolia for the following additional indications:

- Treatment to increase bone mass in men with osteoporosis at high risk for fracture
- Treatment of glucocorticoid-induced osteoporosis in men and women at high risk of fracture
- Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer
- Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer[9]

History of the REMS for Prolia

Prior to the FDA's initial approval of Prolia in 2010, the agency determined that a REMS was necessary to ensure that the benefits of Prolia outweighed the risks of serious infection, dermatologic adverse events, and over-suppression of bone turnover.[10] The FDA approved Amgen's proposed REMS, which included a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS.

The FDA has approved multiple modifications to the REMS since 2010, including the following:

- In June 2012, the addition of the serious risks of hypocalcemia to the Prolia Dear Health Care Provider (DHCP) letter and implementation of steps to increase health care providers' awareness of the importance of the Medication Guide.[11]
- In July 2013, the addition of the risk of hypersensitivity reactions to the Medication Guide.[12]

[8] Food and Drug Administration. Letter to Amgen approving BLA 125320/0 for Prolia. June 1, 2010. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/125320s000Approv.pdf. Accessed April 10, 2019.
[9] Amgen. Label: denosumab (Prolia). May 2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125320s186lbl.pdf. Accessed April 10, 2019.
[10] Food and Drug Administration. Letter to Amgen approving BLA 125320/0 for Prolia. June 1, 2010. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/125320s000Approv.pdf. Accessed April 10, 2019.
[11] Food and Drug Administration. Letter to Amgen approving supplemental BLA 125320/78 for Prolia. June 7, 2012. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/125320s0078ltr.pdf. Accessed April 10, 2019.
[12] Food and Drug Administration. Letter to Amgen approving supplemental BLA 125320/113 for Prolia. July 3, 2013. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2013/125320Orig1s113ltr.pdf. Accessed April 10, 2019.

- In June 2014, the addition of a warning about severe musculoskeletal pain to the Medication Guide.[13]
- In May 2015, the replacement of the DHCP letter with a REMS Letter for Healthcare Providers and a REMS Letter for Professional Societies that highlights the serious risks of Prolia and the importance of providing each patient with a copy of the Medication Guide and Patient Brochure and reviewing this information with the patient; the addition of a Patient Counseling Toolkit that contains a Patient Counseling Tool for Healthcare Providers, a Patient Brochure, and copies of the product labeling and Medication Guide; and dissemination of Prolia REMS-related information at scientific meetings.[14,15]

Product labeling warnings regarding the risk of fractures after cessation of Prolia

In January 2017, the FDA approved the addition to the WARNINGS AND PRECAUTIONS section of Prolia's product labeling of the following new warning about the risk of multiple vertebral fractures following discontinuation of the drug:

> **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) 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 before initiating treatment with Prolia.
>
> If Prolia treatment is discontinued, consider transitioning to an alternative antiresorptive therapy *[see Adverse Reactions (6.1)]*.[16]

[13] Food and Drug Administration. Letter to Amgen approving supplemental BLA 125320/150 for Prolia. June 16, 2014. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2014/125320Orig1s150ltr.pdf. Accessed April 10, 2019.
[14] Food and Drug Administration. Letter to Amgen approving supplemental BLA 125320/162 for Prolia. May 21, 2015. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/125320Orig1s162ltr.pdf. Accessed April 10, 2019.
[15] Amgen. Prolia REMS Letter for Healthcare Providers. May 2015. http://www.proliahcp.com/assets/pdf/rems/Prolia_REMS_Letter_for_Healthcare_Providers.pdf. Accessed April 10, 2019.
[16] Amgen. Label: denosumab (Prolia). May 2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125320s186lbl.pdf. Accessed April 10, 2019.

The FDA-approved Medication Guide also was revised to include the following warning:

> **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.[17]

This petition aims to make this important warning more prominent by moving it to a boxed warning at the front of the product labeling for Prolia. Furthermore, the FDA never required that Amgen prepare and distribute 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 and that describe steps that can be taken to mitigate this risk.[18] As a result, many health care providers and patients likely remain unaware of the serious risk of discontinuing Prolia treatment. Therefore, it is imperative that the FDA immediately require implementation of a modified REMS that includes 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 this risk and that describe steps that can be taken to mitigate it.

3. Overview of Osteoporosis Pathogenesis and Mechanism of Action of Denosumab

Osteoporosis is a skeletal disorder that is characterized by decreased bone mass and strength and a consequently increased risk of bone fractures.[19] It is a complex disease with many different factors contributing to its pathogenesis, including genetics, ethnicity, sex steroid deficiency in postmenopausal women and with aging in men, and underlying diseases that affect the skeletal system, as well as other secondary factors that can cause bone loss, such as corticosteroid use and anorexia.[20]

Under normal, nonpathological states, bone is remodeled continuously through the processes of resorption (bone tissue breakdown) and formation, which are mediated by the two cell types known as osteoclasts and osteoblasts, respectively. Osteoporotic bone loss occurs when bone resorption outpaces bone formation, resulting in failure to replace resorbed bone and net bone

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[17] *Ibid.*

[18] Food and Drug Administration. Approved risk evaluation and mitigation strategies (REMS): Prolia (denosumab). Last update May 21, 2015. https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=IndvRemsDetails.page&REMS=43. Accessed April 10, 2019.

[19] Manolagas SC. Pathogenesis of osteoporosis. *UpToDate.* Updated March 6, 2018. https://www.uptodate.com/contents/pathogenesis-of-osteoporosis. Accessed April 10, 2019.

[20] Khosla S. Pathogenesis of osteoporosis. *Transl Endocinol Metab.* 2010;1(1):55-86.

mass loss. This can be achieved through either the overactivation or increase in the number of osteoclasts or the diminished activation or decrease in the number of osteoblasts.[21]

Estrogen deficiency is a well-recognized critical factor in osteoporosis development in women. Calcium and vitamin D deficiency and secondary hyperparathyroidism also play a role. Increasing evidence shows that other hormones, cytokines, and growth factors also may contribute to the pathogenesis of the disease.[22] Estrogen replacement therapy has been shown to significantly decrease bone turnover and loss in older women.[23]

Inhibition of osteoclastic activation is another mechanism by which osteoporosis progression may potentially be halted. The ligand, receptor activator of nuclear factor kappa-B (NF-κB) ligand (RANKL), is produced by osteoblasts and binds to the receptor activator of NF-κB (RANK), which is expressed on the cell membranes of pre-osteoclasts and osteoclasts.[24] RANKL is essential for normal osteoclast function.[25] The binding of RANKL to RANK promotes osteoclast formation, differentiation, and activation.[26]

Denosumab is a human IgG2 monoclonal antibody that binds to RANKL and prevents it from interacting with its receptor, RANK, thereby inhibiting osteoclast formation, differentiation, and activation and, ultimately, bone resorption, resulting in an increase in cortical and trabecular bone mass.[27] This drug's mechanism of action is similar to that of osteoprotegerin, an endogenous inhibitor of RANKL that is also produced by osteoblasts.[28] Denosumab is the first drug to target the RANKL-RANK pathway.

Prolia is administered subcutaneously at a dose of 60 milligrams (mg) every six months.[29] Patients receiving the drug also should take 1,000 mg of calcium and at least 400 international units of vitamin D daily. Premarket clinical trials demonstrated that compared with a placebo, Prolia significantly reduced the incidence of new vertebral fractures, hip fractures, and nonvertebral fractures and significantly increased bone mineral density (BMD) in the lumbar spine, total hip, and femoral neck in postmenopausal women with osteoporosis; significantly

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[21] Manolagas SC. Pathogenesis of osteoporosis. *UpToDate.* Updated March 6, 2018. https://www.uptodate.com/contents/pathogenesis-of-osteoporosis. Accessed April 10, 2019.

[22] Raisz LG. Pathogenesis of osteoporosis: concepts, conflicts, and prospects. *J Clin Invest.* 2005; 115(12):3318-3325.

[23] Rosen HN, Drezner MK. Postmenopausal hormone therapy in the prevention and treatment of osteoporosis. *UpToDate.* Updated January 23, 2019. Accessed April 10, 2019. https://www.uptodate.com/contents/postmenopausal-hormone-therapy-in-the-prevention-and-treatment-of-osteoporosis. Accessed April 10, 2019.

[24] Food and Drug Administration. Medical reviews for BLA 125320. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/125320s000MedR.pdf. Accessed April 10, 2019. PDF pages 61-62.

[25] *Ibid*.

[26] *Ibid*.

[27] *Ibid*.

[28] *Ibid*.

[29] Amgen. Label: denosumab (Prolia). May 2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125320s186lbl.pdf. Accessed April 10, 2019.

increased BMD in the lumbar spine in men with osteoporosis, women and men with glucocorticoid-induced osteoporosis, and women receiving adjuvant aromatase inhibitor therapy for breast cancer; and significantly reduced the incidence of new vertebral fracture and increased BMD in the lumbar spine in men with nonmetastatic prostate cancer who are receiving androgen deprivation therapy.[30]

4. Human evidence of rapid reversal of denosumab's positive effects and an increased risk of vertebral fractures upon cessation of denosumab treatment

In spite of its effectiveness, denosumab's intended effects on bone metabolism are highly reversible, and there is a significant increase in bone turnover and rapid net bone loss upon discontinuation of the drug.[31,32] Denosumab's mechanism of action is responsible for its reversible nature. Bisphosphonates also target osteoclasts, but unlike denosumab, bisphosphonates have a high affinity for hydroxyapatite crystals and become incorporated into bone tissue.[33,34] Denosumab's effects diminish within months of discontinuation, whereas those of bisphosphonates can persist three to five years after discontinuation.[35]

Data from clinical trials

Miller et al conducted a randomized, blinded, placebo- and active-comparator-controlled phase 2 clinical trial of denosumab in 412 postmenopausal women with low bone mass.[36] The subjects were randomly assigned to receive denosumab every three months (at doses of 6, 14, or 30 mg) or every six months (at doses of 14, 60, 100, or 210 mg), placebo, or open-label alendronate weekly. After 24 months, subjects receiving denosumab either continued to receive denosumab at 60 mg every six months for an additional 24 months, discontinued denosumab for 24 months, or discontinued denosumab for 12 months and then resumed the drug at a dose of 60 mg every six months for 12 months. Changes in BMD and bone turnover markers were assessed over the course of the 48-month trial. Overall, 262 (64 percent) of the 412 subjects completed the 48-month trial. Continuous, long-term denosumab treatment increased BMD at the lumbar spine (9.4% to 11.8%) and total hip (4.0% to 6.1%) and dramatically suppressed bone turnover markers. The effects of denosumab were fully reversible, as evidenced by significant decreases

[30] *Ibid*.
[31] Zanchetta MB, Boailchuck J, Massari F, et al. Significant bone loss after stopping long-term denosumab treatment: a post FREEDOM study. *Osteoporos Int.* 2018;29(1):41-47.
[32] McClung MR, Wagman RB, Miller PD, et al. Observations following discontinuation of long-term denosumab therapy. *Osteoporos Int*. 2017;28(5):1723-1732.
[33] Drake MT, Clarke BL, Khosla S. Bisphosphonates: Mechanism of Action and Role in Clinical Practice. *Mayo Clin Proc.* 2008;83(9): 1032–1045.
[34] Hanley DA, Adachi JD, Brown V. Denosumab: mechanism of action and clinical outcomes. *Int J Clin Pract.* 2012;66(12): 1139–1146.
[35] Laster AJ, Tanner SB. Duration of treatment in postmenopausal osteoporosis: How long to treat and what are the consequences of cessation of treatment? *Rheum Dis Clin North Am.* 2011;37(3):323-336.
[36] Miller PD, Bolognese MA, Lewiecki EM, et al. Effect of denosumab on bone density and turnover in postmenopausal women with low bone mass after long-term continued, discontinued, and restarting of therapy: A randomized blinded phase 2 clinical trial. *Bone.* 2008;43(2):222–229.

in BMD and increases in bone turnover markers within 12 months of discontinuing denosumab. Finally, the decreases in BMD and increases in bone turnover markers following denosumab cessation were rapidly reversed following retreatment with denosumab for 12 months.

To assess the reversibility of denosumab's effects, Bone et al conducted a two-year off-treatment extension study on 128 postmenopausal women with osteoporosis who had received denosumab during a 24-month randomized, double-blind, placebo-controlled phase 3 clinical trial of denosumab (332 subjects had been enrolled in the randomized trial, and 166 had been randomly assigned to each group).[37] During the two-year extension study, the researchers found that BMD in the lumbar spine and hip declined back to baseline levels (i.e., BMD levels prior to the 24-month course of denosumab) at 12 months after cessation of denosumab. Bone et al also found that within three to six months after denosumab cessation, serum bone turnover markers increased to levels that were higher than baseline levels. Serum bone turnover marker levels peaked at six to 12 months after denosumab cessation and returned to baseline at 24 months after cessation.

These findings led to the investigation of whether fracture risk also increased upon denosumab discontinuation. Brown et al conducted a retrospective analysis to assess fracture incidence following discontinuation of denosumab or placebo in subjects who had been enrolled in the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) trial. This trial was a 36-month randomized, double-blind, placebo-controlled pivotal phase 3 clinical trial that compared denosumab with placebo administered every six months in 7,808 postmenopausal women with osteoporosis.[38] The researchers compared fracture rates in subjects who had received two to five doses of either denosumab or placebo in the FREEDOM trial and who had continued participation for at least seven months after receiving their last dose of denosumab or placebo. At least two doses of denosumab were required for a subject to be included in the retrospective analysis because 12 months is the earliest time point at which antifracture efficacy has been observed with denosumab treatment. The off-treatment observation period began seven months after the last dose of denosumab or placebo and continued for up to 24 months. A total of 797 subjects (470 placebo subjects and 327 denosumab subjects) were included in Brown et al's retrospective analysis. The mean follow-up time during the off-treatment period was 0.8 years for both study groups. During the off-treatment period, the fracture rate per 100 subject-years was similar for both groups: 13.5 for the placebo-group subjects and 9.7 for the denosumab-group subjects (adjusted hazards ratio [HR] 0.82; 95% confidence interval [CI], 0.49-1.38). It is important to note that the study had several important limitations, including its post-hoc design, relatively small number of subjects, limited duration of subject follow-up, and the lack of a comparison of fracture rates in the denosumab subjects during treatment and off-treatment. Furthermore, nearly one-third of subjects began a secondary

[37] Bone HG, Bolognese MA, Yuen KC, et al. Effects of denosumab treatment and discontinuation on bone mineral density and bone turnover markers in postmenopausal women with low bone mass. *J Clin Endocrinol Metab.* 2011;96(4):972–980.

[38] Brown JP, Roux C, Törring O, et al. Discontinuation of denosumab and associated fracture incidence: Analysis from the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) trial. *J Bone Miner Res.* 2013;28(4):746–752.

antiresorptive osteoporosis drug during the off-denosumab period, potentially confounding the analysis.

In a study that addressed some of the limitations of the Brown et al analysis, Cummings et al published a more recent retrospective analysis of the rate of new or worsening vertebral fractures in subjects who discontinued denosumab treatment during the FREEDOM trial or its open-label seven-year extension trial.[39] The researchers compared vertebral fracture rates on-treatment and off-treatment in subjects who had received at least two doses of either denosumab or placebo in the FREEDOM trial or its extension trial and who had continued participation for at least seven months. A total of 1,471 subjects (470 placebo subjects and 1,001 denosumab subjects) were included in the Cummings et al retrospective analysis. The median follow-up time during the off-treatment period was 0.5 years (interquartile range [IQR], 0.3-1.4 years) after discontinuing placebo in the FREEDOM trial, 0.5 years (IQR, 0.2-1.4 years) after discontinuing denosumab in the FREEDOM trial, and 0.2 years (IQR, 0.1-0.7 years) after discontinuing denosumab in the FREEDOM extension trial.

Consistent with previous results of the overall FREEDOM trial, Cummings et al found that the rate of vertebral fractures (new or worsening) was lower during the on-treatment period in subjects receiving denosumab compared with those who received a placebo (1.2 [95% CI, 0.9-1.6] versus 7.0 [95% CI, 5.2-8.7] per 100 subject-years, respectively). But after discontinuing denosumab, the rate of vertebral fractures increased to 7.1 (95% CI, 5.2-9.0) per 100 subject-years, which was similar to the rate seen before and after discontinuing placebo (7.0 [95 % CI, 5.2–8.7] and 8.5 [95% CI, 5.5–11.5] per 100 subject-years, respectively). Among the subjects who experienced at least one vertebral fracture after stopping denosumab (n=56) or placebo (n=31), the proportion of subjects who had multiple such fractures was higher in the denosumab group (61 percent) than in the placebo group (39 percent).

Cummings et al concluded the following:

> [D]enosumab substantially reduces the risk of vertebral fractures, and soon after treatment discontinuation, a patient's risk of vertebral fracture returns to the level before treatment initiation. Additionally, more than half of patients who sustain a vertebral fracture have multiple vertebral fractures. Physicians should keep careful track of the dates when a patient's next dose of denosumab is due. If a patient discontinues denosumab, particularly if she has had a vertebral fracture, the patient should promptly receive a bisphosphonate or another antiresorptive agent to prevent the increased risk of vertebral fractures, especially multiple vertebral fractures, that develop soon after stopping denosumab.

[39] Cummings SR, Ferrari S, Eastell R, et al. Vertebral fractures after discontinuation of denosumab: A post hoc analysis of the randomized placebo-controlled FREEDOM Trial and its Extension. *J Bone Miner Res.* 2018;33(2):190-198.

Data from observational studies

McClung et al conducted a one-year observational study of 82 postmenopausal women with osteoporosis who had received denosumab for up to eight years as part of a phase 2 clinical trial.[40] The patients received osteoporosis management at the discretion of their physician. Most (65 [79 percent]) of the patients did not receive prescription osteoporosis medication during the one-year observation period, and 34 of these patients reported that their physician recommended no treatment, most commonly because the doctor felt the patient no longer needed a medication. Of the 17 patients who did receive osteoporosis medications, eight discontinued the treatment during the observation period. In patients treated with denosumab for eight years (n=52), BMD decreased during the one-year observation study (6.7% [lumbar spine], 6.6% [total hip]). Eight of the 82 patients (9.8%) experienced at least one fracture, and seven patients had at least one vertebral fracture. Of the eight patients who experienced a fracture, six had not taken any prescription medication for osteoporosis during the observation study; the other two patients began an osteoporosis medication only after the fracture event occurred.

Zanchetta et al conducted an observational study of 38 elderly women (mean age 81, range 76 to 89) who had participated in the FREEDOM trial and its extension trial at a single site and who did not receive bisphosphonate treatment after discontinuing denosumab.[41] The researchers examined BMD changes and fracture incidence after denosumab cessation. The patients had received denosumab for seven to 10 years and had a follow-up visit 16 to 20 months after the last dose of the drug. The researchers found that BMD had significantly declined in all skeletal regions tested compared with BMD at six months following the last denosumab dose: 8.1 percent decline in the lumbar spine, 6.0 percent decline in the femoral neck, and 8.4 percent decline in the total hip. The patients also had elevated serum bone turnover markers. Five patients (13.2 percent) suffered fragility fractures (one with a wrist fracture and four with vertebral fractures). Of the four patients who sustained vertebral fractures, two had no prior history of fragility fractures, and two had prevalent vertebral fractures.

Data from case series

Additional evidence linking the cessation of denosumab treatment to the occurrence of vertebral fractures is provided by two recently published case series that, combined, included 33 unique

[40] McClung MR, Wagman RB, Miller PD, et al. Observations following discontinuation of long-term denosumab therapy. *Osteoporos Int.* 2017;28(5):1723–1732.

[41] Zanchetta MB, Boailchuk J, Massari F, et al. Significant bone loss after stopping long-term denosumab treatment: a post FREEDOM study. *Osteoporos Int.* 2018;29(1):41-47.

individual cases.[42,43] The first and largest reported case series, published by Anastasilakis et al,[44] included a systematic review of previously published case series and case reports that together totaled 13 postmenopausal women who sustained vertebral fractures after discontinuing denosumab treatment,[45,46,47,48,49] plus a report of eleven additional such patients from the authors' medical centers. The authors of this case series labeled these fractures "rebound-associated vertebral fractures," which refers to vertebral fractures that result from a severe rebound in bone turnover and reversion of BMD to pretreatment baseline levels. The patients had a mean age of 64.1 years (range 48-83). These 24 patients experienced a total of 112 new vertebral fractures following discontinuation of denosumab. Key observations regarding the vertebral fractures included the following:

- The mean and median number of fractures per patient were 4.7 and 5.0, respectively (range one to nine).
- Twenty-two (92 percent) of the patients had two or more vertebral fractures; none experienced nonvertebral fractures during the follow-up period.
- The most common location of fracture was vertebra T12, which was observed in 17 patients, followed by L1 (14 patients), L3 (13 patients), T11 (12 patients), and L2 (12 patients).
- The mean duration denosumab treatment was 2.9 years (range one to five years), which corresponds to approximately six doses.
- Patients with two years or less of denosumab treatment had fewer post-treatment fractures than those with more than two years of treatment (mean ± standard error: 3.2 ± 0.7 versus 5.2 ± 1.4, respectively; $p = 0.055$)
- The mean time interval between the final denosumab injection and the occurrence of the first vertebral fracture was 11.2 months (range eight to 16 months). Considering that the effects of denosumab last about six months following injection, the adjusted mean time

[42] Anastasilakis AD, Polyzos SA, Makras P, et al. Clinical features of 24 patients with rebound-associated vertebral fractures after denosumab discontinuation: systematic review and additional cases. *J Bone Miner Res.* 2017;32(6):1291–1296.

[43] Tripto‐Shkolnik L, Rouach V, Marcus Y et al. Vertebral fractures following denosumab discontinuation in patients with prolonged exposure to bisphosphonates. *Calcif Tissue Int.* 2018;103(1):44-49.

[44] Anastasilakis AD, Polyzos SA, Makras P, et al. Clinical features of 24 patients with rebound-associated vertebral fractures after denosumab discontinuation: systematic review and additional cases. *J Bone Miner Res.* 2017;32(6):1291–1296.

[45] Aubry-Rozier B, Gonzalez-Rodriguez E, Stoll D, Lamy O. Severe spontaneous vertebral fractures after denosumab discontinuation: three case reports. *Osteoporos Int.* 2016;27(5):1923–1925.

[46] Lamy O, Gonzalez-Rodriguez E, Stoll D, et al. Severe rebound-associated vertebral fractures after denosumab discontinuation: 9 clinical cases report. *J Clin Endocrinol Metab.* 2017;102(2):354–358.

[47] Anastasilakis AD, Makras P. Multiple clinical vertebral fractures following denosumab discontinuation. *Osteoporos Int.* 2016;27(5):1929–1930.

[48] Popp AW, Zysset PK, Lippuner K. Rebound-associated vertebral fractures after discontinuation of denosumab-from clinic and biomechanics. *Osteoporos Int.* 2016;27(5):1917–1921.

[49] Polyzos SA, Terpos E. Clinical vertebral fractures following denosumab discontinuation. *Endocrine.* 2016;54(1):271–272.

between the point at which the drug was effectively discontinued and the occurrence of the first fracture was approximately five months (range two to 10 months).

- Five patients underwent vertebroplasty for their post-denosumab vertebral fractures. The procedures were unsuccessful in all cases, with all patients sustaining new vertebral fractures.

Additional notable observations for the Anastasilakis et al case series included the following:

- Eight (33 percent) of the patients had prevalent vertebral fractures prior to stopping denosumab, and one of these patients also had a prevalent hip fracture.
    - Four of these patients had single vertebral fractures (T8, T12, L1, and L2)
    - Two patients had two vertebral fractures each, one at T11 and L1 and the other at L3 and L5
    - One patient had three fractures at T7, T10, and T12
    - One patient had five prevalent fractures at T6, T7, T12, T13, and L4

- Most of the patients (20 of 24, 83 percent) were osteoporosis treatment naïve prior to treatment with denosumab.
- Of the four patients who had received osteoporosis therapy before treatment with denosumab, two were treated with bisphosphonates (one for three years, 11 years prior to initiating denosumab; one for a very brief duration), one with strontium ranelate for one year and raloxifene for five years, and one with teriparatide for one year.
- Five patients had a history of breast cancer and were taking an aromatase inhibitor, which can increase the risk of bone fracture.[50]
- One woman had a history of secondary hyperparathyroidism, and one patient had rheumatoid arthritis but never took glucocorticoids.
- Only one patient was taking glucocorticoids for an inflammatory disease.
- The reported reasons for discontinuing denosumab were the following:
    - BMD increased to the osteopenic (nine patients) or normal range (four patients, three of whom also completed treatment with an aromatase inhibitor)
    - Treatment duration (three patients)
    - Patient's wish (three patients)
    - Treatment omission (two patients)
    - End of aromatase inhibitor treatment (one patient)
    - Dental treatment (one patient)
    - Patient negligence (one patient)

Anastasilakis et al concluded that it is most important to enhance physicians' awareness of the risk of bone fragility and vertebral fractures following discontinuation of denosumab treatment and that patients should not delay or omit doses of denosumab. They further emphasized that "denosumab discontinuation should be carefully considered and, if decided, another anti-

[50] Byreddy DV, Bouchonville MF, Lewiecki EM. Drug-induced osteoporosis: from Fuller Albright to aromatase inhibitors. *Climacteric*. 2015;18(Suppl 2):39-46.

osteoclastic treatment should be administered to avoid bone turnover rebound followed by increased risk of fractures."

The second recent case series, published by Tripto-Shkolnik et al, comprised nine elderly postmenopausal women in Israel who had experienced rebound-associated vertebral fractures after discontinuation of denosumab treatment.[51] The authors of this case series were particularly interested in examining cases involving patients who had received bisphosphonates prior to treatment with denosumab because prior treatment with bisphosphonates had been postulated to decrease the risk of rebound-associated vertebral fractures following discontinuation of denosumab treatment.[52] The nine patients had a mean (± standard deviation [SD]) age of 74.2 ± 5.3 years (range 68-81). Six of the patients had been treated with bisphosphonates for a mean (± SD) of 7.4 ± 3.2 years prior to denosumab treatment. A seventh patient had been treated with bisphosphonates for four years and then teriparatide for two years prior to denosumab treatment.

The nine patients experienced a total of 36 new vertebral fractures following discontinuation of denosumab. Key observations regarding the vertebral fractures included the following:

- The mean and median number of fractures per patient were both 4.0 (range one to nine).
- Eight (89 percent) of the patients had two or more vertebral fractures.
- All fractures were symptomatic, and most were spontaneous.
- The most common location of the fractures was vertebra T12, observed in five patients, followed by T11, L1, L2, and L3 (four patients each).
- The mean (± SD) number of denosumab doses was 4.9 ± 1.6 (range three to eight).
- The mean time interval between the time of final denosumab injection and the occurrence of the first vertebral fracture was 12.6 months (range seven to 21 months).[53] Considering that the effects of denosumab last about six months following injection, the adjusted mean time between the point at which the drug was effectively discontinued and the occurrence of the first fracture was approximately 6.6 months (range one to 15 months).
- One patient underwent a vertebroplasty for an L3 vertebral fracture and several weeks later presented with vertebral collapse at T8, T12, L1, and L2.

Additional notable observations for the Tripto-Shkolnik et al case series included the following:

- The patients had a mean (± SD) fracture risk assessment tool score of 30 ± 12% for major osteoporotic fractures and 17 ± 11% for hip fractures, which were indicative of a high risk.

[51] Tripto-Shkolnik L, Rouach V, Marcus Y, et al. Vertebral fractures following denosumab discontinuation in patients with prolonged exposure to bisphosphonates. *Calcif Tissue Int.* 2018;103(1):44-49.
[52] Uebelhart B, Rizzoli R, Ferrari SL. Retrospective evaluation of serum CTX levels after denosumab discontinuation in patients with or without prior exposure to bisphosphonates. *Osteoporos Int.* 2017;28(9):2701-2705.
[53] Tripto-Shkolnik et al reported time from the "missed" denosumab dose to the time of the rebound-associated vertebral fractures. We added six months to these reported time intervals to calculate the mean time interval between the time of final denosumab injection and the occurrence of the first vertebral fracture.

- Eight (89 percent) of the nine patients had prevalent osteoporotic fractures prior to the initiation of denosumab (eight vertebral fractures in six patients, distal radius fractures in two patients, and other non-vertebral fractures in two patients).
- The reported reasons for discontinuing denosumab were the following:
    - Physician decision (four patients)
    - Administrative (one patient)
    - Non-osteoporosis-related medical condition (three patients)
    - Unknown (one patient)

The Tripto-Shkolnik et al case series is unique in that most of the patients were not osteoporosis-treatment naïve, with seven having received prior bisphosphonate treatment, which appears to contradict a prior hypothesis that previous exposure to bisphosphonates is protective against rebound-associated vertebral fractures after discontinuation of denosumab treatment.[54] Tripto-Shkolnik et al concluded that health care providers, patients, and regulatory authorities should be aware of the risks of denosumab treatment interruption and consider a course of antiresorptive therapy following cessation of such treatment.

There is substantial, well-documented and increasing evidence from the clinical trials, observational studies, and case series discussed above that the cessation of denosumab treatment causes a significant rapid increase in the risk of rebound-associated vertebral fractures. In particular, given that (a) denosumab's mechanism of action is rapidly reversible and (b) BMD rapidly decreases to pretreatment baseline levels and bone turnover markers rapidly increase to levels exceeding pretreatment baseline levels following cessation of denosumab, it is highly biologically plausible that the cessation of denosumab treatment causes a significant increase in the risk of vertebral fractures. In addition, the retrospective analyses of data from the randomized, placebo-controlled FREEDOM trial and its long-term extension trial that were published in 2018 by Cummings et al demonstrated that after discontinuing denosumab, the rate of vertebral fractures quickly rebounded to a level that was similar to the rates seen before and after discontinuing placebo.[55]

The recently published case series by Anastasilakis et al [56] and by Tripto‑Shkolnik et al[57] revealed several alarming trends in patients who experienced vertebral fractures following cessation of denosumab treatment. First, the mean number of vertebral fractures that occurred following cessation of denosumab treatment was very high (≥ 4 fractures/person). Such multiple

[54] Uebelhart B, Rizzoli R, Ferrari SL. Retrospective evaluation of serum CTX levels after denosumab discontinuation in patients with or without prior exposure to bisphosphonates. *Osteoporos Int.* 2017;28(9):2701-2705.
[55] Cummings SR, Ferrari S, Eastell R, et al. Vertebral fractures after discontinuation of denosumab: A post hoc analysis of the randomized placebo-controlled FREEDOM Trial and its Extension. *J Bone Miner Res.* 2018;33(2):190-198.
[56] Anastasilakis AD, Polyzos SA, Makras P, et al. Clinical features of 24 patients with rebound-associated vertebral fractures after Denosumab discontinuation: systematic review and additional cases. *J Bone Miner Res.* 2017;32(6):1291–1296.
[57] Tripto‑Shkolnik L, Rouach V, Marcus Y, et al. Vertebral fractures following denosumab discontinuation in patients with prolonged exposure to bisphosphonates. *Calcif Tissue Int.* 2018;103(1):44-49.

vertebral fractures can lead to significant pain and disability. Second, the interval between the cessation of treatment (i.e., six months after the last denosumab dose) and occurrence of the vertebral fractures was very short (as short as one month). Third, many of the patients discontinued the drug based on their improved BMD and subsequent recommendations by their physicians, presumably based on the misperceptions that further treatment with Prolia, or any other antiresorptive treatment, was no longer necessary[58] and that it was safe to discontinue treatment. Fourth, treatment of the fractures with vertebroplasty failed in all six cases in which it was attempted, resulting in additional vertebral fractures within a month of the procedure in all cases. Another important observation from these case series is that prevalent fractures appears to be a risk factor for new vertebral fractures after denosumab treatment, as 33 percent of women in the first case series and 66 percent in the second had experienced fractures prior to denosumab initiation.

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. This adverse reaction clearly constitutes a serious injury — so serious in proportion to the potential benefit from the drug that it must be considered an important component of assessing the risks and benefits of the drug.[59] In addition, this is the type of adverse reaction that can be prevented or reduced in severity by appropriate use of the drug.[60] A boxed warning is especially warranted in this case 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.

Implementation of an updated REMS for Prolia is also necessary to ensure that the drug's benefits outweigh its risks. The updated REMS should include the preparation and distribution of an updated 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 and describe steps that can be taken to mitigate this risk. In a health care environment in which patients often transition, sometimes suddenly, from one physician to another because of changes in health insurance coverage, relocation to another region of the country, or physician retirement, it is imperative that patients receiving denosumab understand the risk of missing a scheduled dose of the drug or discontinuing treatment without receiving alternative antiresorptive therapy.

Physicians and patients also need to understand that vertebroplasty may well be a poor option for treating vertebral fractures that occur soon after cessation of denosumab.

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[58] McClung MR. Cancel the denosumab holiday. *Osteoporos Int*. 2016. 27(5);1677-1682.

[59] Food and Drug Administration. 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. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075096.pdf. Accessed April 10, 2019.

[60] *Ibid.*

For these reasons, we hereby petition the FDA, under Sections 352 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 352) and FDA regulations at 21 C.F.R. §§10.30 and 201.56, to take the following actions: under Section 352 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 352) and under FDA regulations at 21 C.F.R. §§ 10.30 and 201.56) to immediately require the following:

(1) The addition of a boxed warning to the product labeling of Prolia describing the risk of vertebral fractures upon drug discontinuation. We suggest the following wording for the requested boxed warning:

> **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 cases 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)]*.**

Conforming changes also should be made in other sections of the product labeling.

(2) Implementation of an updated REMS for Prolia that includes 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, Patient Brochure, and Medication Guide that highlight the risk of multiple vertebral fractures following discontinuation of Prolia treatment and that describe steps that can be taken to mitigate this risk. The updated REMS should require that the Patient Brochure be given to patients every time they receive a dose of Prolia. The updated 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.

III. ENVIRONMENTAL IMPACT

We claim categorical exclusion under 21 C.F.R. § 25.31(a) from the environmental assessment requirement. An assessment is not required because the requested action would not increase the use of the active moiety that is the subject of this petition.

IV. ECONOMIC IMPACT

Will be submitted upon request.

V. CERTIFICATIONS

We certify that, to the best of our knowledge and belief, this petition includes all information and views on which this petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

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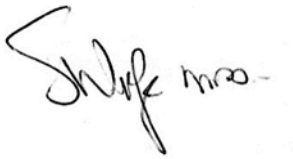

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