

BL 125320 PROLIA[®] (denosumab)

Amgen Inc.
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RISK EVALUATION AND MITIGATION STRATEGY (REMS)

1. Goals

To inform healthcare providers (HCP) and patients about the risks of hypocalcemia, serious infections, dermatologic adverse reactions, and suppression of bone turnover, including osteonecrosis of the jaw and atypical femoral fractures, associated with Prolia® (denosumab).

2. REMS Elements

2.1 Medication Guide

Amgen will ensure the Prolia Medication Guide is distributed in accordance with 21CFR 208.24.

The Medication Guide is part of the REMS and is appended.

2.2 Communication Plan

Amgen will implement a communication plan (CP) to inform Healthcare Providers (HCP) about the risks of hypocalcemia, serious infections, dermatologic adverse reactions, and suppression of bone turnover, including osteonecrosis of the jaw and atypical femoral fractures, associated with Prolia.

The CP consists of a Dear Healthcare Provider (DHCP) Letter, which will be sent by electronic mailing or mass mailing within 60 days of the most recent REMS approval to endocrinologists; rheumatologists; obstetricians/gynecologists; primary care physicians who received the first DHCP letter or had written at least 1 prescription for an osteoporosis medication since the launch of Prolia; oncologists and urologists who are likely to prescribe or have prescribed hormone ablation as a method of treatment for patients with prostate or breast cancer; and to any known new prescribers of Prolia who were not previously sent the DHCP Letter. If a targeted HCP's email address is not available, or if an email is undeliverable, the provider will receive the letter through the mail. The DHCP Letter will be sent to the following professional societies within 60 days of the most recent REMS approval requesting they provide this letter to their members: National Osteoporosis Foundation, American Society of Bone Mineral Research, American College of Rheumatology, American Association of Clinical Endocrinologists, the American College of Physicians, the American Academy of Family Physicians, the Endocrine Society, and the American Society of Clinical Oncology. A copy of the US Prescribing Information and Medication Guide will accompany the DHCP Letter.

Amgen will resend the DHCP Letter to the following professional societies annually from the date of the initial REMS approval (6/2010) for 3 years: National Osteoporosis Foundation, American Society of Bone Mineral Research, American College of Rheumatology, American Association of Clinical Endocrinologists, the American College of Physicians, the American Academy of Family Physicians, the Endocrine Society, and the American Society of Clinical Oncology.

The DHCP Letter, US Prescribing Information, and Medication Guide will also be distributed to HCPs via sales representatives and medical science liaisons at the time of initial contact, when inquired about the risks outlined in the REMS, or upon request; through the Amgen toll-free medical information line (1-800-772-6436); and through a REMS-dedicated link [www.proliahcp.com] from the website.

The Medication Guide, DHCP Letter, and web page are part of the REMS and are appended.

3. Timetable for Submission

Amgen will submit REMS Assessments to FDA at 18 months, 3 years, and 7 years from the date of the initial approval (01 June 2010) of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Amgen will submit each assessment so that it will be received by the FDA on or before the due date.



IMPORTANT DRUG WARNING

SUBJECT: Serious risks associated with the use of Prolia

- **Hypocalcemia**
- **Serious infections**
- **Suppression of bone turnover, including osteonecrosis of the jaw and atypical femoral fractures** (New Safety Information)
- **Dermatologic adverse events**

Insert Date

Dear Healthcare Provider:

Amgen would like to remind you about the risks of **hypocalcemia, serious infections, dermatologic adverse reactions, and suppression of bone turnover**, including **osteonecrosis of the jaw** (ONJ) and to communicate the risk of **atypical femoral fracture**, associated with the use of Prolia[®] (denosumab). Prolia has a risk evaluation mitigation strategy (REMS) required by the FDA because of these risks.

- **Hypocalcemia:** Hypocalcemia may be exacerbated by the use of Prolia. Pre-existing hypocalcemia must be corrected prior to initiating therapy with Prolia. Adequately supplement all patients with calcium and vitamin D. Particular attention should be paid to those at increased risk of hypocalcemia (e.g., severe renal impairment including those receiving dialysis). Consider the benefit-risk profile when administering Prolia to patients at increased risk of hypocalcemia.
- **Serious infections:** In a clinical trial of women with postmenopausal osteoporosis, serious infections leading to hospitalization were reported more frequently in the Prolia group than in the placebo group. Serious skin infections, as well as infections of the abdomen, urinary tract, and ear, were more frequent in patients treated with Prolia.
- **Suppression of bone turnover (including osteonecrosis of the jaw (ONJ), fracture healing complications, and atypical femoral fractures):** Prolia results in significant suppression of bone remodeling. The long-term consequences of the degree of suppression of bone remodeling observed with Prolia may contribute to adverse outcomes such as ONJ, atypical femoral fractures and delayed fracture healing. Other conditions posing a risk for developing ONJ include invasive dental procedures and poor oral hygiene.

Cases of atypical femoral fracture have been confirmed in patients receiving Prolia. Atypical femoral fractures are subtrochanteric or proximal diaphyseal fractures that occur with little to no trauma and may be bilateral. Specific radiographic findings, including a simple transverse or oblique fracture with beaking of the cortex and diffuse cortical thickening of the proximal femoral shaft, characterize these events.¹ During Prolia treatment, patients should be advised

to report new or unusual thigh, hip, or groin pain. As appropriate, evaluate for an incomplete femoral fracture and examine the contralateral femur.

- **Dermatologic adverse events:** In a clinical trial of women with postmenopausal osteoporosis, epidermal and dermal adverse events such as dermatitis, eczema, and rashes occurred at a significantly higher rate in the Prolia group compared to the placebo group.

Prolia contains the same active ingredient (denosumab) found in XGEVA[®]. Patients should not be treated with Prolia and XGEVA at the same time.

Prolia is indicated for: (1) treatment of postmenopausal women with osteoporosis at high risk for fracture, (2) treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer, (3) treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer, and (4) treatment to increase bone mass in men with osteoporosis at high risk for fracture.

Please read the accompanying FDA-approved full [prescribing information](#) for Prolia. Prolia has a [Medication Guide](#) that accompanies the Full Prescribing Information. You should review the information in the Medication Guide with your patients. Provide each patient with a Medication Guide every time you administer Prolia to your patients as the information contained within may change over time.

To report **Suspected Adverse Reactions**, contact Amgen Inc. at 1-800-77-AMGEN (1-800-772-6436) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Sincerely,

Michael Severino, MD
Senior Vice President, Global Development and Chief Medical Officer
Amgen

¹. Shane E, Burr D, Ebeling PR, et al. Atypical subtrochanteric and diaphyseal femoral fractures: report of a task force of the American Society of Bone and Mineral Research. *J Bone Miner Res.* 2010;25:2267-2294.