
Initial REMS Approval: 06/01/10 Most

Recent Modification: 10/2019

BL 125320 PROLIA® (denosumab)

Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
805-447-1000

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

1. Goals

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:

- a. informing 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®
- b. informing healthcare providers they should counsel patients about the risks associated with PROLIA®.

2. REMS Elements

2.1 Medication Guide

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

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

2.2 Communication Plan

Amgen will implement the following communication plan to healthcare providers likely to prescribe PROLIA®. The communication plan will include:

2.2.1 REMS Letters

Amgen will send a REMS Letter for Healthcare Providers and REMS Letter for Professional Societies within 60 calendar days of this REMS modification and again 1 year after approval of this REMS modification. The REMS Letters will address potential risks of (1) hypocalcemia, (2) osteonecrosis of the jaw, (3) atypical femoral fractures, (4) serious infections, and (5) dermatologic reactions associated with PROLIA®.

The REMS Letter for Healthcare Providers will be distributed by US mail. If the REMS Letter for Healthcare Providers is undeliverable, Amgen will use available resources to obtain updated address information and send a second letter via US mail within 45 calendar days of return. If the correct address cannot be obtained, the attempt will be documented and no further communication will occur.

The REMS Letter for Professional Societies will be sent as an attachment to an email. If the email is undeliverable or marked as unopened, a second email will be sent within 7 calendar days. If the second email is undeliverable or marked as unopened, the REMS letter will be mailed within 30 calendar days.

A copy of, or a link to, the Prescribing Information (PI) and Medication Guide will accompany each REMS Letter.

REMS Letter for Healthcare Providers

The intended audience for the REMS Letter for Healthcare Providers will be endocrinologists, rheumatologists, obstetricians/gynecologists, primary care physicians, oncologists, and urologists.

The REMS Letter for Healthcare Providers will also be available via a link from the PROLIA® REMS website, through Amgen's Medical Information Department, and from Amgen's sales and/or medical representatives upon request for one year after the approval of this REMS modification (05/2015).

REMS Letter for Professional Societies

Amgen will send the REMS Letter for Professional Societies to the following professional societies and organizations requesting the letter or its content be provided to their membership.

- National Osteoporosis Foundation
- American Society of Bone Mineral Research
- American College of Rheumatology

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- American Association of Clinical Endocrinologists
 - American Academy of Family Physicians
 - Endocrine Society
 - American Society of Clinical Oncology
 - North American Menopause Society

2.2.2 Patient Counseling Toolkit

Amgen will provide healthcare providers with a Patient Counseling Toolkit, including a Patient Counseling Chart for Healthcare Providers, a Patient Brochure, and copies of the PI and Medication Guide. Throughout the duration of the REMS, the contents of the Patient Counseling Toolkit will be detailed to targeted healthcare providers (eg, endocrinologists, rheumatologists, obstetricians/gynecologists, primary care physicians, oncologists, urologists) where Amgen has sales representatives deployed to speak with healthcare providers in the field. These targeted healthcare providers include prescribers who are likely to prescribe PROLIA®.

Patient Counseling Chart for Healthcare Providers

Amgen will provide a Patient Counseling Chart for Healthcare Providers, which will be a standalone tool for healthcare providers to counsel patients. Amgen sales or medical representatives will verbally discuss the risk messages contained in the Patient Counseling Chart for Healthcare Providers during the visit with the healthcare provider.

Patient Brochure

The Patient Brochure includes information on risk messages and will be provided to healthcare provider offices as an additional counseling tool for patients.

2.2.3 Journal Information Piece

Amgen will publish a journal information piece quarterly for 12 months after approval of the REMS modification (05/2015) in the following professional journals:

- Journal of the American Medical Association
- Arthritis and Rheumatology
- Endocrine Today

2.2.4 Dissemination of REMS Information at Scientific Meetings

The PROLIA® REMS Patient Counseling Toolkit will be prominently displayed at relevant scientific meetings where Amgen has a PROLIA® commercial booth presence for the duration of the REMS.

2.2.5 REMS Website

The PROLIA® REMS website for healthcare professionals (www.proliahcp.com/risk-evaluation-mitigation-strategy) will continue for the duration of the REMS. The REMS website will include the option to print versions of the PI, Medication Guide, REMS Letter for Healthcare Providers, Patient Counseling Chart for Healthcare Providers, Patient Brochure, and journal information piece. The PROLIA® product website will include a prominent REMS-specific link to PROLIA® REMS website. All website information will be updated within 60 days post approval of the modification.

The following are part of the PROLIA® REMS and are appended:

- REMS Letter for Healthcare Providers
- REMS Letter for Professional Societies
- Patient Counseling Chart for Healthcare Providers
- Patient Brochure
- Journal Information Piece
- REMS Website (landing page)

3. Timetable for Submission of Assessments

Amgen will submit REMS Assessments to FDA at 18 months, 3, 6, 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 will 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.



PROLIA[®] REMS

FDA Required REMS Safety Information

Serious Risks Associated with Prolia[®] (denosumab)

- Hypocalcemia
- Osteonecrosis of the Jaw
- Atypical Femoral Fractures
- Serious Infections
- Dermatologic Reactions

Month YYYY

Important Safety Update

Dear Healthcare Provider:

The FDA has required this safety update as part of the PROLIA[®] REMS (**R**isk **E**valuation and **M**itigation **S**trategy) to inform healthcare providers about the following **serious risks of Prolia[®]**:

Hypocalcemia

- Hypocalcemia may be exacerbated by the use of Prolia[®].

Osteonecrosis of the Jaw

- Osteonecrosis of the jaw (ONJ) has been reported in patients receiving Prolia[®].

Atypical Subtrochanteric and Diaphyseal Femoral Fractures

- Atypical low-energy or low trauma subtrochanteric and diaphyseal femoral fractures, which may be bilateral, have been reported in patients receiving Prolia[®]. Atypical femoral fractures most commonly occur with minimal or no trauma to the affected area.

Serious Infections

- In a clinical trial, women with postmenopausal osteoporosis treated with Prolia[®] presented with serious infections, such as serious skin infection and endocarditis, leading to hospitalization more frequently than the placebo group.

Dermatologic Reactions

- In a clinical trial, women with postmenopausal osteoporosis treated with Prolia[®] presented with generalized epidermal and dermal adverse events at a significantly higher rate compared to the placebo group. These included dermatitis, eczema, and rashes.

Role of the Healthcare Provider

- ✓ **Make note** of these risks and discuss them with your patients using the non-promotional **Patient Counseling Toolkit**, which includes:
 - **Patient Counseling Chart for Healthcare Providers**
 - **Patient Brochure**
 - **Prescribing Information**
 - **Medication Guide**
- Note: these materials are available to order through 1-800-77-AMGEN (1-800-772-6436), by downloading the information from www.proliahcp.com/risk-evaluation-mitigation-strategy, or by contacting your local Amgen Sales Representative.
- ✓ **Review** information in the **Medication Guide and Patient Counseling Chart** with your patients, including the serious risks of Prolia[®] and the symptoms of each risk.
- ✓ **Advise** each patient to seek prompt medical attention if they have signs or symptoms of any of the serious risks.
- ✓ **Provide** each patient a copy of the **Medication Guide** and **Patient Brochure**.
- ✓ **Visit** www.proliahcp.com/risk-evaluation-mitigation-strategy for more information about the Prolia[®] REMS.

Indication

Prolia[®] is a RANK ligand (RANKL) inhibitor indicated for the:

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

This letter does not contain the complete safety profile for Prolia[®]. Please review the Prescribing Information and Medication Guide, enclosed.

Reporting Adverse Events

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088. Healthcare providers should report all suspected adverse events associated with Prolia[®] to the FDA or to Amgen at 1-800-772-6436.

Sincerely,

Isma Benattia, MD
Vice President, Global Patient Safety
Amgen

[Attachment of the Prolia[®] Prescribing Information and Medication Guide]



PROLIA[®] REMS

FDA Required REMS Safety Information

Serious Risks Associated with Prolia[®] (denosumab)

- Hypocalcemia
- Osteonecrosis of the Jaw
- Atypical Femoral Fractures
- Serious Infections
- Dermatologic Reactions

Month YYYY

Important Safety Update

Dear [Professional Society]:

The FDA has required Amgen to distribute this safety update to your organization as part of our PROLIA[®] REMS (**R**isk **E**valuation and **M**itigation **S**trategy) program. We request that you inform your members about the following **serious risks of Prolia[®]**:

Hypocalcemia

- Hypocalcemia may be exacerbated by the use of Prolia[®].

Osteonecrosis of the Jaw

- Osteonecrosis of the jaw (ONJ) has been reported in patients receiving Prolia[®].

Atypical Subtrochanteric and Diaphyseal Femoral Fractures

- Atypical low-energy or low trauma subtrochanteric and diaphyseal femoral fractures, which may be bilateral, have been reported in patients receiving Prolia[®]. Atypical femoral fractures most commonly occur with minimal or no trauma to the affected area.

Serious Infections

- In a clinical trial, women with postmenopausal osteoporosis treated with Prolia[®] presented with serious infections, such as serious skin infection and endocarditis, leading to hospitalization more frequently than the placebo group.

Dermatologic Reactions

- In a clinical trial, women with postmenopausal osteoporosis treated with Prolia[®] presented with generalized epidermal and dermal adverse events at a significantly higher rate compared to the placebo group. These included dermatitis, eczema, and rashes.

Role of the Healthcare Provider

- ✓ **Make note** of these risks and discuss them with your patients using the non-promotional **Patient Counseling Toolkit**, which includes:
 - [Patient Counseling Chart for Healthcare Providers](#)
 - [Patient Brochure](#)
 - [Prescribing Information](#)
 - [Medication Guide](#)

Note: These materials are available to order through 1-800-77-AMGEN (1-800-772-6436) or by downloading the information from www.proliahcp.com/risk-evaluation-mitigation-strategy.

- ✓ **Review** information in the **Medication Guide and Patient Counseling Chart** with each patient, including the serious risks of Prolia[®] and the symptoms of each risk.
- ✓ **Advise** each patient to seek prompt medical attention if they have signs or symptoms of any of the serious risks.
- ✓ **Provide** each patient a copy of the **Medication Guide** and **Patient Brochure**.
- ✓ **Visit** www.proliahcp.com/risk-evaluation-mitigation-strategy for more information about the Prolia[®] REMS.

Indication

Prolia[®] is a RANK ligand (RANKL) inhibitor indicated for the:

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

This letter does not contain the complete safety profile for Prolia[®]. Please visit www.proliahcp.com/risk-evaluation-mitigation-strategy for more information about Prolia[®] and the Prolia[®] REMS Program. A link to the full Prescribing Information is provided where risks associated with Prolia[®] are clearly outlined.

Reporting Adverse Events

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088. Healthcare providers should report all suspected adverse events associated with Prolia[®] to the FDA or to Amgen at 1-800-772-6436.

Sincerely,

Isma Benattia, MD
Vice President, Global Patient Safety
Amgen

Prolia[®] (denosumab): Patient Counseling Chart for Healthcare Providers

Prolia® (denosumab): What Patients Need to Know

What is Prolia®?

Prolia® is a prescription medicine used to:

- Treat osteoporosis in women after menopause who:
 - are at high risk for fracture
 - cannot use another osteoporosis medicine or other osteoporosis medicines did not work well
- Increase bone mass in men with osteoporosis who are at high risk for fracture
- Treat bone loss in men who are at high risk for fracture receiving certain treatments for prostate cancer that has not spread to other parts of the body
- Treat bone loss in women who are at high risk for fracture receiving certain treatments for breast cancer that has not spread to other parts of the body

What side effects can Prolia® (denosumab) have?

Prolia® can cause serious side effects including:

- Low calcium levels in your blood (see page 4)
- Severe jaw bone problems (osteonecrosis) (see page 5)
- Unusual thigh fractures (see page 6)
- Serious infections (see page 7)
- Skin problems (see page 8)

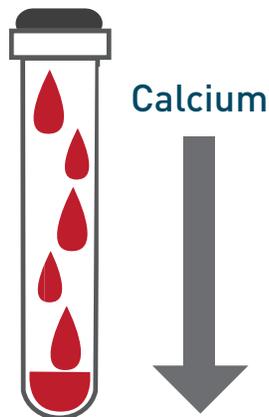
Please talk about these side effects with your doctor.



Call your doctor right away if you think you may be having any of these side effects.

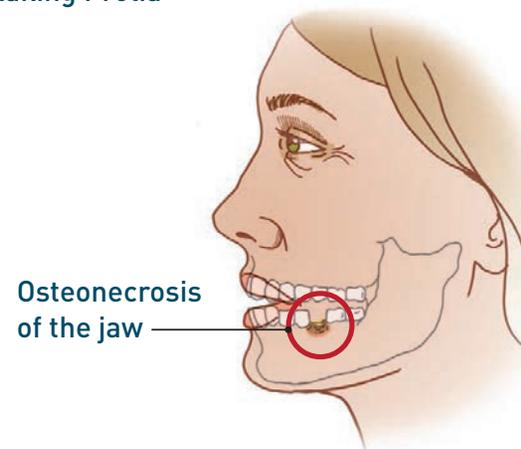
Low calcium levels in your blood

- Prolia® may lower the calcium levels in your blood
- Symptoms of low blood calcium include:
 - Spasms, twitches, or cramps in your muscles
 - Numbness or tingling in your fingers, toes, or around your mouth
- If you have low blood calcium before you start receiving Prolia®, it may get worse during treatment
- Your low blood calcium must be treated before you receive Prolia®
- Your doctor may prescribe calcium and vitamin D to help prevent low calcium levels in your blood while you take Prolia®. Take calcium and vitamin D as your doctor tells you to



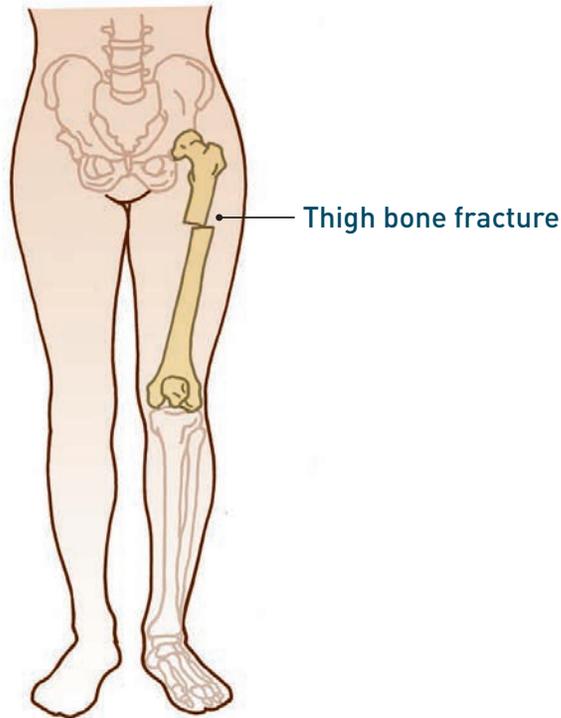
Severe jaw bone problems (osteonecrosis)

- Severe jaw bone problems (osteonecrosis of the jaw or ONJ) may happen when you take Prolia®
- ONJ is a potentially serious condition that can be seen as a sore in the mouth through which the jaw bone is sometimes visible. The jaw bone and gum tissue over the bone may heal slowly or not heal at all
- The most common risk factor associated with ONJ is tooth extraction. It is important for you to practice good mouth care during treatment with Prolia®
- See your dentist regularly for check-ups and cleaning
- Tell your dentist you are taking Prolia® or will start taking Prolia®



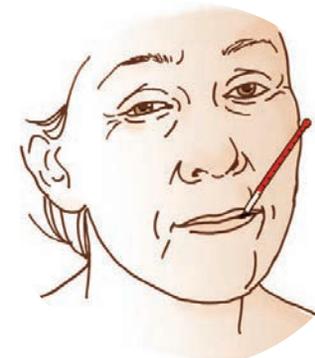
Unusual thigh fractures

- Some people have developed unusual fractures in their thigh bone
- Symptoms of thigh bone fracture include new or unusual pain in your hip, groin, or thigh



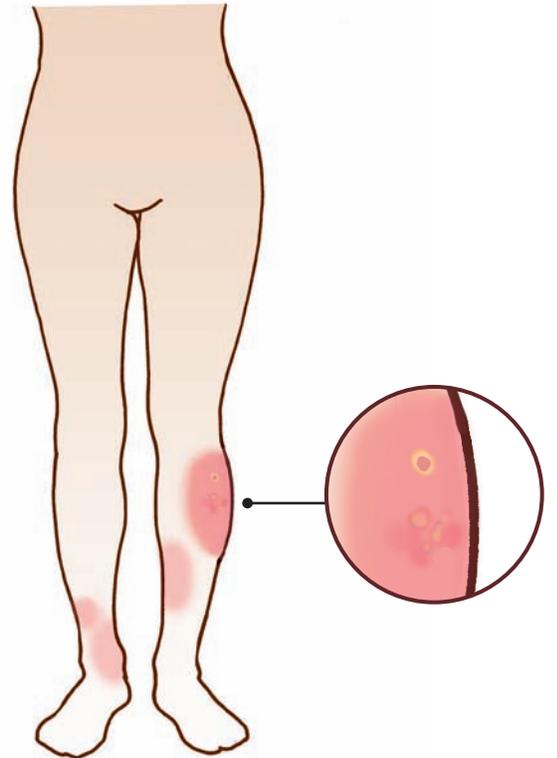
Serious infections

- Prolia® is a medicine that may affect the ability of your body to fight infections
- Serious infections in your skin, lower stomach area (abdomen), bladder, or ear may happen if you take Prolia®
- Inflammation of the inner lining of the heart (endocarditis) due to an infection also may happen more often in people who take Prolia®
- Symptoms of some serious infections include:
 - Fever or chills
 - Skin that looks red or swollen and is hot or tender to touch
 - Fever, shortness of breath, cough that will not go away
 - Frequent or urgent need to urinate or burning feeling when you urinate



Skin problems

- Skin problems may happen if you take Prolia®
- Symptoms of skin problems include:
 - Dermatitis (redness, itching)
 - Eczema (leathery dry skin, blisters that ooze or become crusty, skin peeling)



Call your doctor right away if you think you may be having any of these side effects.



Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
www.amgen.com

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Prolia® (denosumab) Guide for Patients: Important Things YOU Need to Know

What is Prolia®?

Prolia® is a prescription medicine used to:

- Treat osteoporosis (thinning and weakening of bone) in women after menopause (“change of life”) who:
 - are at high risk for fracture (broken bone)
 - cannot use another osteoporosis medicine or other osteoporosis medicines did not work well
- Increase bone mass in men with osteoporosis who are at high risk for fracture
- Treat bone loss in men who are at high risk for fracture receiving certain treatments for prostate cancer that has not spread to other parts of the body
- Treat bone loss in women who are at high risk for fracture receiving certain treatments for breast cancer that has not spread to other parts of the body

What side effects can Prolia® have?

Prolia® can cause serious side effects that all patients taking Prolia® must know.

Please talk about these side effects with your doctor.

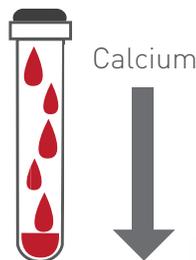


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The side effects can include:

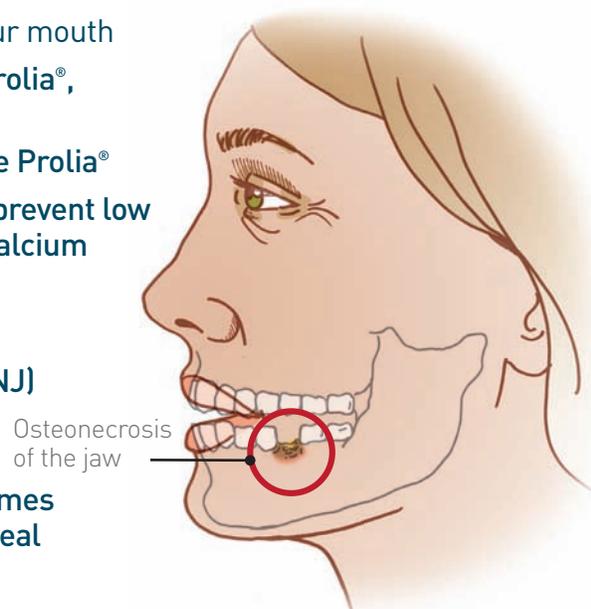
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- If you have low blood calcium before you start receiving Prolia®, it may get worse during treatment
- Your low blood calcium must be treated before you receive Prolia®
- Your doctor may prescribe calcium and vitamin D to help prevent low calcium levels in your blood while you take Prolia®. Take calcium and vitamin D as your doctor tells you to



Severe jaw bone problems (osteonecrosis)

- Severe jaw bone problems (**osteonecrosis of the jaw or ONJ**) may happen when you take Prolia®
- ONJ is a potentially serious condition that can be seen as a sore in the mouth through which the jaw bone is sometimes visible. The jaw bone and gum tissue over the bone may heal slowly or not heal at all



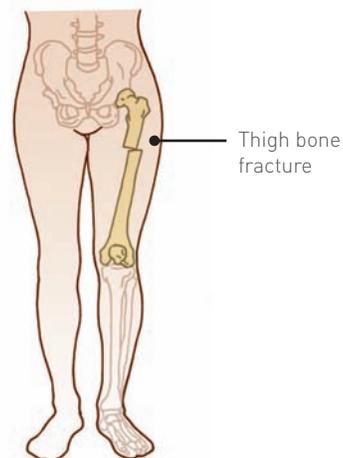
Side effects are continued on back.

Severe jaw bone problems (osteonecrosis) cont.

- The most common risk factor associated with ONJ is tooth extraction. It is important for you to practice good mouth care during treatment with Prolia®
- See your dentist regularly for check-ups and cleaning
- Tell your dentist you are taking Prolia® or will start taking Prolia®

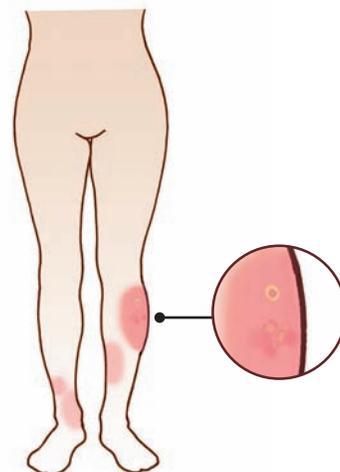
Unusual thigh fractures

- Some people have developed unusual fractures in their thigh bone
- Symptoms of thigh bone fracture include new or unusual pain in your hip, groin, or thigh



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- Serious infections in your skin, lower stomach area (abdomen), bladder, or ear may happen if you take Prolia®
- Inflammation of the inner lining of the heart (endocarditis) due to an infection also may happen more often in people who take Prolia®
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Skin problems

- Skin problems may happen if you take Prolia®
- Symptoms of skin problems include:
 - Dermatitis (redness, itching)
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Call your doctor right away if you think you may be having any of these side effects.



Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
www.amgen.com

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FDA REQUIRED REMS Safety Information for Prolia[®] (denosumab)

Serious Risks Associated with Prolia[®]:

Hypocalcemia and Mineral Metabolism

Hypocalcemia may be exacerbated by the use of Prolia[®]. In patients predisposed to hypocalcemia and disturbances of mineral metabolism, clinical monitoring of calcium and mineral levels is highly recommended.

Osteonecrosis of the Jaw

Osteonecrosis of the Jaw (ONJ) has been reported in patients receiving Prolia[®]. ONJ, which can occur spontaneously, is generally associated with tooth extraction and/or local infection with delayed healing.

Atypical Subtrochanteric and Diaphyseal Femoral Fractures

Atypical low-energy or low trauma subtrochanteric and diaphyseal femoral fractures, which may be bilateral, have been reported in patients receiving Prolia[®]. Atypical femoral fractures most commonly occur with minimal or no trauma to the affected area.

Serious Infections

In a clinical trial, women with postmenopausal osteoporosis treated with Prolia[®] presented with serious infections, such as infections of the abdomen, urinary tract, and ear, as well as endocarditis.

Dermatologic Reactions

In a clinical trial, women with postmenopausal osteoporosis treated with Prolia[®] presented with generalized epidermal and dermal adverse events at a significantly higher rate compared to the placebo group.

Role of the Healthcare Provider

- ✓ **Review** information in the Prolia[®] Medication Guide and Patient Counseling Chart with each patient, including the serious risks of Prolia[®] and the symptoms of each risk.
- ✓ **Advise** each patient to seek prompt medical attention if they have signs or symptoms of any of the serious risks.
- ✓ **Provide** each patient a copy of the Medication Guide and Patient Brochure.

Prolia[®] is Indicated for the:

- Treatment of postmenopausal women with osteoporosis at high risk for fracture
- Treatment to increase bone mass in men with osteoporosis at high risk for 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

Reporting Adverse Events

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088. Healthcare providers should report all suspected adverse events associated with Prolia[®] to the FDA or to Amgen at 1-800-772-6436.

This journal information piece is part of the FDA-required Prolia[®] REMS. Visit www.proliahcp.com/risk-evaluation-mitigation-strategy for more information.

For complete safety information, see the Prescribing Information available at www.proliahcp.com/risk-evaluation-mitigation-strategy.



Prolia® (denosumab) Risk Evaluation and Mitigation Strategy

What is the Prolia® REMS?

A REMS (Risk Evaluation and Mitigation Strategy) is a program required by the Food and Drug Administration to manage known or potential serious risks associated with a drug product.

The purpose of the Prolia® REMS is to inform healthcare providers and patients about the following serious risks of:

- ▶ Hypocalcemia
- ▶ Osteonecrosis of the jaw
- ▶ Atypical femoral fractures
- ▶ Serious infections
- ▶ Dermatologic reactions

The Prolia® REMS program materials are designed to inform healthcare providers and patients about these risks with Prolia®. They include a REMS Letter for Healthcare Providers, Patient Counseling Chart for Healthcare Providers, Patient Brochure, Journal Information Piece, Prescribing Information, and Medication Guide. It is important that you discuss with your patients the information included in the Patient Counseling Chart for Healthcare Providers, the Patient Brochure, and the Medication Guide.

To learn more about the serious risks of Prolia®, read the [Important Safety Information](#) provided in this link and use the links on the right to access REMS supporting materials.

Reporting Adverse Events

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088. Healthcare providers should report all suspected adverse events associated with Prolia® to the FDA or to Amgen at 1-800-772-6436.

Materials for Healthcare Providers

 [REMS Letter for Healthcare Providers ▶](#)

 [Journal Information Piece ▶](#)

Patient Counseling Toolkit

 [Patient Counseling Chart for Healthcare Providers ▶](#)

 [Patient Brochure ▶](#)

 [Prescribing Information ▶](#)

 [Medication Guide ▶](#)

Materials for Patients

 [Patient Brochure ▶](#)

 [Medication Guide ▶](#)

