BL 125320 PROLIA® (denosumab)

Amgen Inc.
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RISK EVALUATION AND MITIGATION STRATEGY (REMS)

1. Goals

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

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 serious infections, dermatologic adverse reactions, and suppression of bone turnover, including osteonecrosis of the jaw, associated with Prolia.

The CP consists of a Dear Healthcare Provider (DHCP) Letter, which will be sent within 60 days of the most recent REMS approval to 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 by mass mailing or electronic mailing. Amgen will obtain HCP email addresses from the American Medical Association (AMA). 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. A copy of the US Prescribing Information and Medication Guide will accompany the DHCP Letter.

The DHCP Letter will be sent to the American Society of Clinical Oncology within 60 days of the most recent REMS approval requesting they provide this letter to their members.

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.

Any known new prescribers of Prolia who were not previously sent the DHCP Letter will be sent a DHCP Letter for up to 2 years from the date of the initial REMS approval. New prescribers of Prolia will be identified using the Healthcare Professional Data Management database, obtained from Intercontinental Marketing Services (IMS).

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 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 (June 1, 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
Regarding Prolia (denosumab)

Subject: **Risk of serious infections, dermatologic adverse events and suppression of bone turnover with use of Prolia**

<Insert date>

Dear Healthcare Provider:

Amgen would like to inform you of important safety information for Prolia™ (denosumab), which has been approved by the US Food and Drug Administration (FDA). Prolia is indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. Prolia reduces the incidence of vertebral, non-vertebral and hip fractures.

Important Information about the Risks of Prolia

The FDA has approved Prolia with a Risk Evaluation and Mitigation Strategy (REMS) to ensure the benefits of the drug outweigh the risks of:

- **serious infections,**
- **dermatologic adverse events and**
- **suppression of bone turnover.**

Serious infections

In a clinical trial of over 7800 women with postmenopausal osteoporosis, serious infections leading to hospitalization were reported more frequently in the Prolia group than in the placebo group. Serious infections including skin infections and endocarditis, as well as infections of the abdomen, urinary tract and ear, were more frequent in patients treated with Prolia.

Dermatologic adverse events

Epidermal and dermal adverse events such as dermatitis, eczema and rashes occurred at a significantly higher rate in the Prolia group (10.8%) compared to the placebo group (8.2%).

Suppression of bone turnover (including osteonecrosis of the jaw (ONJ) and fracture healing complications)

Prolia results in significant suppression of bone remodeling as evidenced by markers of bone turnover and bone histomorphometry. The long-term consequences of the degree of suppression of bone remodeling observed with Prolia may contribute to adverse outcomes such as ONJ, atypical fractures and delayed fracture healing. ONJ has been reported in the osteoporosis clinical trial in patients receiving denosumab.

Introduction of Prolia Post-marketing Active Safety Surveillance Program

To monitor the long-term safety of Prolia, Amgen will be soliciting adverse event reporting of 9 pre-specified adverse events of special interest (AESI) including serious infections, dermatologic adverse events and suppression of bone turnover. Data collection will include an AESI soliciting questionnaire and AESI-specific questionnaire. Prolia prescribers are invited to

MEDICATION GUIDE

Prolia® (PRÓ-lee-a)

(denosumab)
Injection, for subcutaneous use

Read the Medication Guide that comes with Prolia before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or treatment. Talk to your doctor if you have any questions about Prolia.

What is the most important information I should know about Prolia?

If you receive Prolia, you should not receive XGEVA®. Prolia contains the same medicine as Xgeva (denosumab).

Prolia can cause serious side effects including:

1. **Low calcium levels in your blood (hypocalcemia).**
   Prolia may lower the calcium levels in your blood. 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. Most people with low blood calcium levels do not have symptoms, but some people may have symptoms. Call your doctor right away if you have symptoms of low blood calcium such as:
   - Spasms, twitches, or cramps in your muscles
   - Numbness or tingling in your fingers, toes, or around your mouth

   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.

2. **Serious 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. You may need to go to the hospital for treatment if you develop an infection.

   Prolia is a medicine that may affect your immune system. People who have weakened immune system or take medicines that affect the immune system may have an increased risk for developing serious infections.

   Call your doctor right away if you have any of the following symptoms of infection:
   - Fever or chills
   - Skin that looks red or swollen and is hot or tender to touch
   - Severe abdominal pain
   - Frequent or urgent need to urinate or burning feeling when you urinate

3. **Skin problems.**
   Skin problems such as inflammation of your skin (dermatitis), rash, and eczema may happen if you take Prolia. Call your doctor if you have any of the following symptoms of skin problems that do not go away or get worse:
   - Redness
   - Itching
   - Small bumps or patches (rash)
   - Your skin is dry or feels like leather
   - Blisters that ooze or become crusty
   - Skin peeling

4. **Severe jaw bone problems (osteonecrosis).**
   Severe jaw bone problems may happen when you take Prolia. Your doctor should examine your mouth before you start Prolia. Your doctor may tell you to see your dentist before you start Prolia. It is important for you to practice good mouth care during treatment with Prolia.

Call your doctor right away if you have any of these side effects.

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.
- 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.

It is not known if Prolia is safe and effective in children.

Who should not take Prolia?

Do not take Prolia if you:

- have been told by your doctor that your blood calcium level is too low.
- are pregnant or plan to become pregnant
- are allergic to denosumab or any of the ingredients in Prolia. See the end of this leaflet for a complete list of ingredients in Prolia.

What should I tell my doctor before taking Prolia?

Before taking Prolia, tell your doctor if you:

- Are taking a medicine called Xgeva (denosumab). Xgeva contains the same medicine as Prolia.
- Have low blood calcium.

- Cannot take daily calcium and vitamin D.
- Had parathyroid or thyroid surgery (glands located in your neck).
- Have been told you have trouble absorbing minerals in your stomach or intestines (malabsorption syndrome).
- Have kidney problems or are on kidney dialysis.
- Plan to have dental surgery or teeth removed.
- Are pregnant or plan to become pregnant. Prolia may harm your unborn baby. Tell your doctor right away if you become pregnant while taking Prolia.
    - **Pregnancy Surveillance Program:** Prolia is not intended for use in pregnant women. If you become pregnant while taking Prolia, talk to your doctor about enrolling in Amgen's Pregnancy Surveillance Program or call 1-800-772-6436 (I-800-77-AMGEN). The purpose of this program is to collect information about women who have become pregnant while taking Prolia.
- Are breastfeeding or plan to breastfeed. It is not known if Prolia passes into your breast milk. You and your doctor should decide if you will take Prolia or breastfeed. You should not do both.

Tell your doctor about all the medicines you take, including prescription and nonprescription drugs, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of medicines with you to show to your doctor or pharmacist when you get a new medicine.

How will I receive Prolia?

- Prolia is an injection that will be given to you by a healthcare professional. Prolia is injected under your skin (subcutaneous).
- You will receive Prolia 1 time every 6 months.
- You should take calcium and vitamin D as your doctor tells you to while you receive Prolia.
- If you miss a dose of Prolia, you should receive your injection as soon as you can.
- Take good care of your teeth and gums while you receive Prolia. Brush and floss your teeth regularly.
- Tell your dentist that you are receiving Prolia before you have dental work.

What are the possible side effects of Prolia?

Prolia may cause serious side effects.

- See **"What is the most important information I should know about Prolia?"**
- **Long-term effects on bone:** It is not known if the use of Prolia over a long period of time may cause slow healing of broken bones or unusual fractures.

The most common side effects of Prolia in women who are being treated for osteoporosis after menopause are:

- back pain
- pain in your arms and legs
- high cholesterol
- muscle pain
- bladder infection

The most common side effects of Prolia in patients receiving certain treatments for prostate or breast cancer are:

- joint pain
- back pain
- pain in your arms and legs
- muscle pain

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of Prolia. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Prolia if I need to pick it up from a pharmacy?

- Keep Prolia in a refrigerator at 36°F to 46°F (2°C to 8°C) in the original carton.
- Do not freeze Prolia.
- When you remove Prolia from the refrigerator, Prolia must be kept at room temperature [up to 77°F (25°C)] in the original carton and must be used within 14 days.
- Do not keep Prolia at temperatures above 77°F (25°C). Warm temperatures will affect how Prolia works.
- Do not shake Prolia.
- Keep Prolia in the original carton to protect from light.

Keep Prolia and all medicines out of reach of children.

General information about Prolia.

Do not give Prolia to other people even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about Prolia. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about Prolia that is written for health professionals.

For more information, go to www.Prolia.com or call Amgen at 1-800-772-6436.

What are the ingredients in Prolia?
Active ingredient: denosumab
Inactive ingredients: sorbitol, acetate, polysorbate 20 (prefilled syringe only), Water for Injection (USP), and sodium hydroxide

Amgen Manufacturing Limited, a subsidiary of Amgen Inc.
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Thousand Oaks, California 91320-1799

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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voluntarily participate in this study and are encouraged to register and may do so online, by mail or by fax.

Medication Guide

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.

Reporting Patient Adverse Events

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.

Read the accompanying FDA-approved full prescribing information for Prolia. We urge you to contact our Medical Information department at 1-800-772-6436 or visit www.proliahcp.com if you have any questions about the information contained in this letter or the safe and effective use of PROLIA.

Sean E. Harper, MD
Senior Vice President, Global Development
and Chief Medical Officer
Amgen Inc.

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/s/

AUDREY L GASSMAN
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