

**ENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125320

REMS

Risk Evaluation and Mitigation Strategy (REMS)

Prolia™ (denosumab)

Prepared by:

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

1. Goals

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

2. REMS Elements

2.1 Medication Guide

Under 21 CFR 208.24, Amgen will ensure the Prolia Medication Guide is distributed with each unit-of-use for HCPs to dispense to each patient who is administered Prolia.

Prolia will be provided in unit-of-use packaging dispensed for single patient use. Every Prolia unit-of-use package will include the US Prescribing Information and Medication Guide.

The carton and container package will include a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed.

Please see the approved Medication Guide in Appendix 1.

2.2 Communication Plan

Amgen will implement a communication plan to healthcare providers to support implementation of this REMS within 60 days of approval of the REMS and/or in conjunction with launch of Prolia, whichever is sooner.

The communication plan consists of a Dear Healthcare Provider (DHCP) Letter (Appendix 2).

Initially, the DHCP Letter will be sent by mass mailing or electronic mailing to targeted endocrinologists, rheumatologists, gynecologists, and primary care physicians who have written at least one prescription for an osteoporosis medication in the last 12 months. Amgen will send the DHCP Letter electronically to physicians for whom email addresses are available. Amgen will purchase available email addresses from the American Medical Association (AMA). Targeted providers whose email addresses are not

available from the AMA will receive the DHCP letter through US mail. This letter will be sent within 60 days of approval of the REMS and/or in conjunction with launch of Prolia, whichever is sooner. The field force will make the DHCP Letter available to HCPs at the time of initial contact. The DHCP Letter will also be available through a REMS-dedicated link from the [www.proliahcp.com] website. (See attached web page in Appendix 3.)

In addition, Amgen will distribute the DHCP Letter to the following professional societies: 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, and the Endocrine Society. Amgen will request that these societies provide the letter to their membership. Following initial distribution, the DHCP Letter will be sent to these professional societies annually for up to 3 years after approval, again with a request that they provide the letter to their membership.

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 after approval of the REMS or Prolia launch. New prescribers will be identified using the Healthcare Professional Data Management database, obtained from Intercontinental Marketing Services (IMS). DHCP Letters will be sent to any new prescribers identified who were not sent a DHCP letter previously.

The DHCP Letter will convey important information to providers on the risks associated with the use of Prolia, including the risks of serious infections, dermatologic adverse reactions, and suppression of bone turnover. The mailing will also include a copy of the Prescribing Information and the Medication Guide. These materials will also be available upon request via sales and/or clinical representatives and/or through the Amgen toll-free medical information line (1-800-772-6436).

These materials will also be available through a REMS-dedicated link from the [www.proliahcp.com] website.

3. Elements to Assure Safe Use

The REMS for Prolia does not include Elements to Assure Safe Use.

4. Implementation System

The REMS for Prolia does not include Elements to Assure Safe Use. Therefore an Implementation System is not required.

5. Timetable for Submission

Amgen will submit REMS Assessments to FDA at 18 months, 3 years and 7 years from the date of the approval 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.

MEDICATION GUIDE

Prolia™ (PRÓ-lee-a)

(*denosumab*)

Injection

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?

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

- have an increased risk for fractures (broken bones).
- cannot use another osteoporosis medicine or other osteoporosis medicines did not work well.

Who should not receive Prolia?

Do not take Prolia if you have been told by your doctor that your blood calcium level is too low.

What should I tell my doctor before receiving Prolia?

Before taking Prolia, tell your doctor if you:

- 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 with Amgen’s Pregnancy Surveillance Program, or call 1-800-772-6436 (1-800-77-AMGEN). The purpose of this program is to collect information about women who have become pregnant while taking Prolia.

- Are breast-feeding or plan to breast-feed. It is not known if Prolia passes into your breast milk. You and your doctor should decide if you will take Prolia or breast-feed. 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 are:

- Back pain
- Pain in your arms and legs
- High cholesterol
- Muscle pain
- Bladder infection

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 handle 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.

What is osteoporosis?

Osteoporosis is a disease in which the bones become thin and weak, increasing the chance of having a broken bone. Osteoporosis usually causes no symptoms until a fracture happens. The most common fractures are in the spine (backbone). They can shorten height, even without causing pain. Over time, the spine can become curved or deformed and the body bent over. Fractures from osteoporosis can also happen in almost any bone in the body, for example, the wrist, rib, or hip. Once you have had a fracture, the chance for more fractures greatly increases.

The following risk factors increase your chance of getting fractures from osteoporosis:

- Past broken bones from osteoporosis.
- Very low bone mineral density (BMD).
- Frequent falls.
- Limited movement, such as using a wheelchair.
- Medical conditions likely to cause bone loss, such as some kinds of arthritis.
- Taking steroid medicines called glucocorticoids, such as prednisone
- Other medicines that may cause bone loss, for example: seizure medicines (such as phenytoin), blood thinners (such as heparin), high doses of vitamin A.

What can I do to treat osteoporosis?

There are many steps you can take to treat osteoporosis. Taking Prolia, along with calcium and vitamin D, may be one option for you.

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

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

Issued: MM/YYYY

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 skin infections, as well as infections of the abdomen, urinary tract, and ear, were more frequent in patients treated with Prolia. Endocarditis was also reported more frequently in the Prolia-treated subjects.

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 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

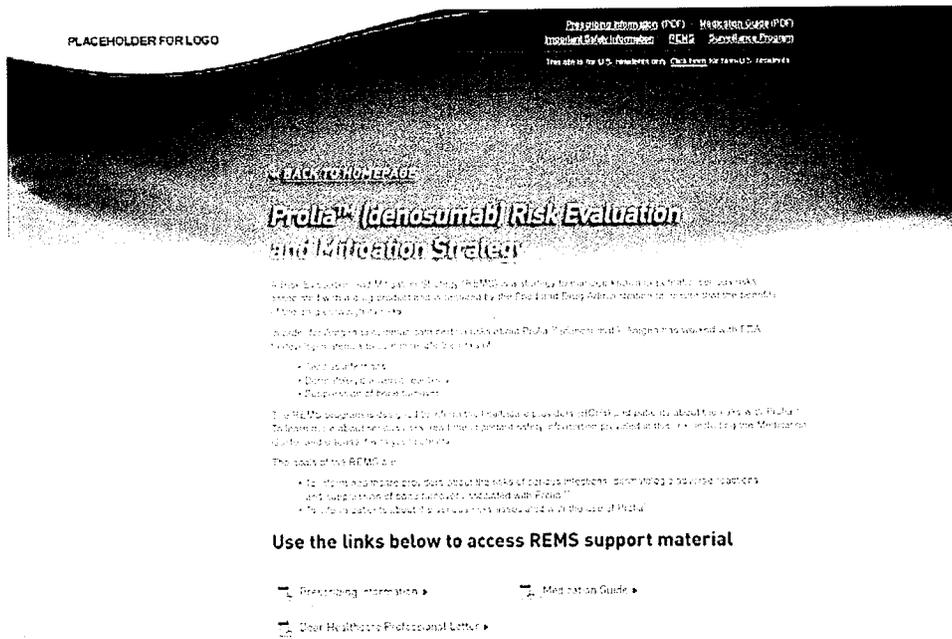
To report SUSPECTED ADVERSE REACTIONS, contact Amgen Inc. at 1-800-77-AMGEN (1-800-772-6436) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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.

Appendix 3. Screenshot of REMS Webpage



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AMGEN®

prolia[™]
(denosumab)



ATTENTION: Dispense the accompanying Medication Guide to each patient. For more copies see www.prolia.com or call 1-877-562-4111.

U.S. License No. 1080
U.S. Patent Nos. 6,740,522,
7,097,834; 7,364,736; 7,411,050

AMGEN®



prolia[™]
(denosumab)

60 mg/mL Injection – For Subcutaneous Use Only.
Single Use Prefilled Syringe. Discard unused portion.

Each prefilled syringe contains: 60 mg denosumab, 17 mM acetate, 0.01% polysorbate 20, sodium hydroxide to a pH of 5.2, 4.7% sorbitol, Water for Injection, USP.

No U.S. standard of potency
See Package Insert for Full Prescribing and Manufacturing Information



NDC 55513-710-01

1 x 60 mg Single Use Prefilled Syringe

AMGEN®

prolia[™]
(denosumab)



60 mg/mL Injection – For Subcutaneous Use Only.
Single Use Prefilled Syringe. Discard unused portion.

Sterile Solution – No Preservative.
Refrigerate at 2° to 8°C (36° to 46°F). Do not freeze. Avoid excessive shaking. Protect from direct light and heat.
This Product Contains Dry Natural Rubber.

Manufactured by: Amgen Manufacturing Ltd., a subsidiary of Amgen Inc. Thousand Oaks, CA 91320-7799

Lot

FPO 2

FPO 2

11899

U.S. License No. 1080
U.S. Patent Nos. 6,740,522;
7,097,894; 7,364,736; 7,411,050

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AMGEN®

prolia
(denosumab)

60 mg/mL



AMGEN®

prolia
(denosumab)

60 mg/mL



60 mg/mL Injection – For Subcutaneous Use Only.
Single Use Prefilled Syringe. Discard unused portion.

Each prefilled syringe contains: 60 mg denosumab, 17 mM acetate, 0.01% polysorbate 20, sodium hydroxide to a pH of 5.2, 4.7% sorbitol. Water for Injection, USP.

No U.S. standard of potency

See Package Insert for Full Prescribing and Manufacturing Information



5 10014 6199 3

1 x 60 mg Single Use Prefilled Syringe

MDC 55513-710-01

AMGEN®

prolia
(denosumab)

60 mg/mL



60 mg/mL Injection – For Subcutaneous Use Only.
Single Use Prefilled Syringe. Discard unused portion.

Sterile Solution – No Preservative.

Refrigerate at 2° to 8°C (36° to 46°F). Do not freeze. Avoid excessive shaking. Protect from direct light and heat.

This Product Contains Dry Natural Rubber.

Manufactured by: Amgen Manufacturing Ltd., a subsidiary of Amgen Inc. Thousand Oaks, CA 91320-1799 Made in Germany

Lot

FP0 2



FP0 2

AMGEN®

prolia
(denosumab)

60 mg/mL



FP01 Barcode
w/ human readable

ONCE
EVERY 6
MONTHS

 **prolia**[™]
(denosumab)

/...../.....
NEXT INJECTION DATE

Thank you for taking Prolia. We can help remind you when you are due for your next treatment. Please visit www.prolia.com or call 1-888-PROLIA6 to sign up for a free reminder program.

11495

AMGEN®

60 mg/mL



prolia[™]
(denosumab)

60 mg/mL
Injection – For Subcutaneous Use Only.
Single Use Prefilled Syringe
Discard unused portion.
Sterile Solution – No Preservative.
Amgen Mfg Ltd.

1 x 60 mg Single Use Prefilled Syringe NDC 55513-710-01

Each prefilled syringe contains: 60 mg denosumab, 17 mM acetate, 0.01% polysorbate 20, sodium hydroxide to a pH of 5.2, 4.7% sorbitol, Water for Injection, USP.

Refrigerate at 2° to 8°C (36° to 46°F). Do not freeze.

Avoid excessive shaking. Protect from direct light and heat.

This Product Contains Dry Natural Rubber.

Dosage – See Package Insert

No U.S. standard of potency

U.S. License No. 1080



Rx Only

11902

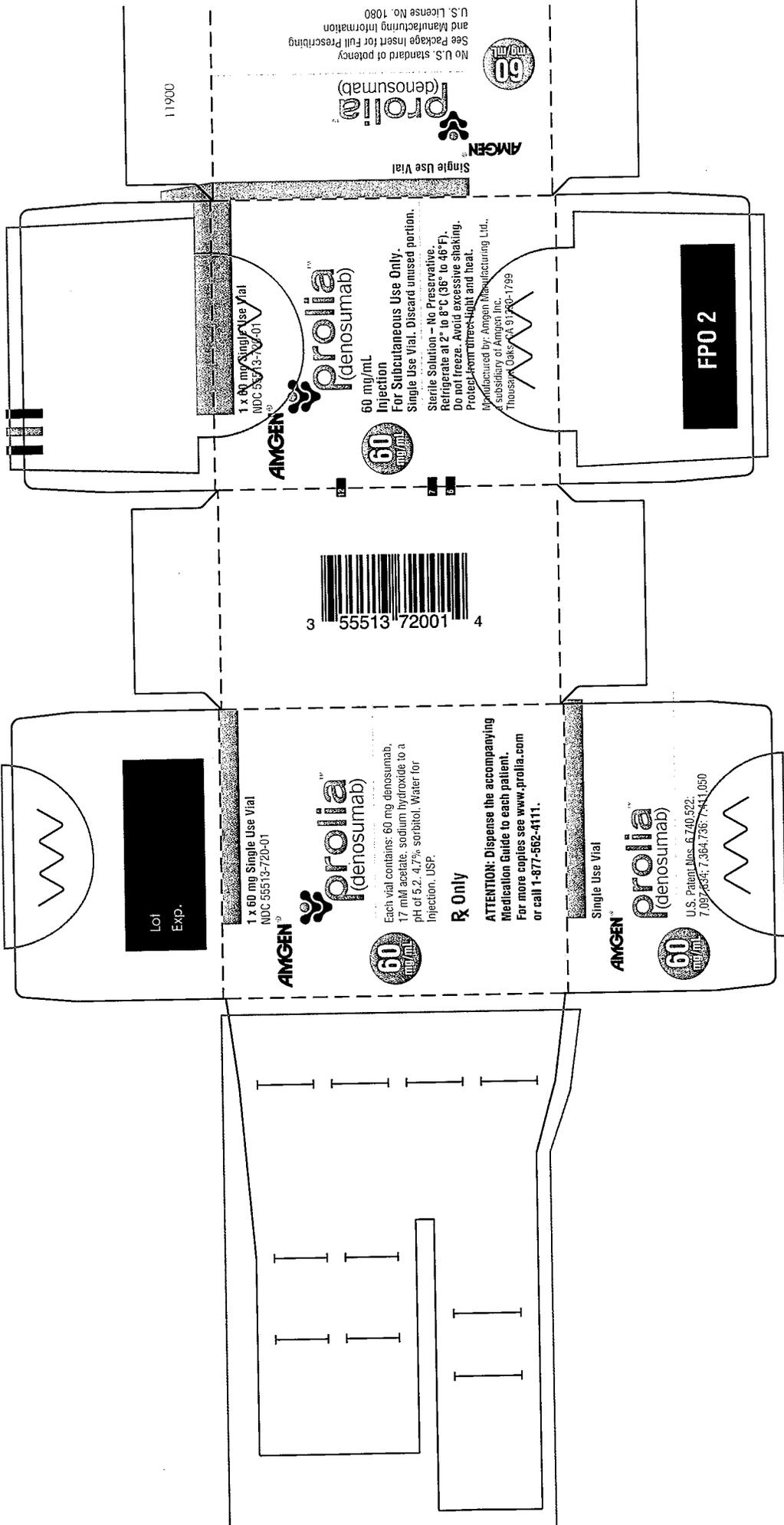
Lot
Exp.

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prolia[™]
60 mg/100 mL
Injection - For Subcutaneous Use Only
R-Only
Roche Products, Inc. U.S. License # 141023
Roche Products, Inc. U.S. License # 141023

EMD
LCC



11900

No U.S. standard of potency
and Manufacturing Information
See Package Insert for Full Prescribing
U.S. License No. 1080

prolia
(denosumab)



Single Use Vial

1 x 60 mg/mL Single Use Vial
NDC 55513-720-01

AMGEN

prolia
(denosumab)

60 mg/mL

Injection

For Subcutaneous Use Only.

Single Use Vial. Discard unused portion.

Sterile Solution - No Preservative.

Refrigerate at 2° to 8°C (36° to 46°F).

Do not freeze. Avoid excessive shaking.

Protect from direct light and heat.

Manufactured by Amgen Manufacturing Ltd.,

A subsidiary of Amgen Inc.,

Thousand Oaks, CA 91320-1799



FPO 2



1 x 60 mg Single Use Vial
NDC 55513-720-01

AMGEN

prolia
(denosumab)



Each vial contains: 60 mg denosumab,
17 mM acetate, sodium hydroxide to a
pH of 5.2-4.7%, sorbitol, Water for
Injection, USP.

Rx Only

ATTENTION: Dispense the accompanying

Medication Guide to each patient.

For more copies see www.prolia.com

or call 1-877-562-4111.

Single Use Vial

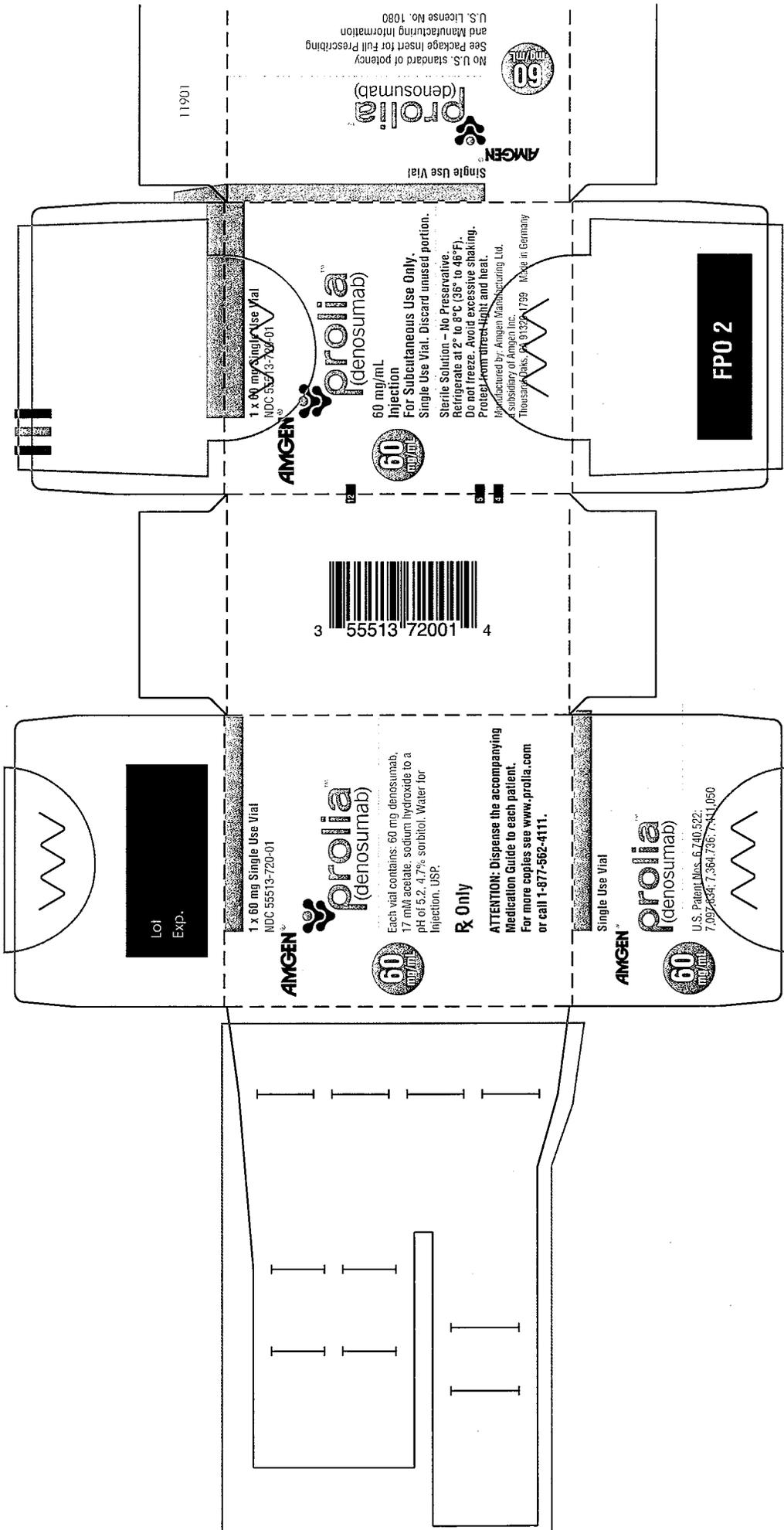
AMGEN

prolia
(denosumab)



U.S. Patent Nos. 6,740,522,
7,097,634; 7,364,736; 7,441,050

Lot
Exp.



AMGEN
prolia
(denosumab)
60 mg/mL
Single Use Vial
No U.S. standard of potency
See Package Insert for Full Prescribing
and Manufacturing Information
U.S. License No. 1080

11901

1 x 60 mg Single Use Vial
NDC 55513-720-01

AMGEN
prolia
(denosumab)
60 mg/mL
Injection

For Subcutaneous Use Only.
Single Use Vial. Discard unused portion.
Sterile Solution - No Preservative.
Refrigerate at 2° to 8°C (36° to 46°F).
Do not freeze. Avoid excessive shaking.
Protect from ~~light~~ light and heat.

Made by Amgen Manufacturing Ltd.
Subsidiary of Amgen Inc.
Thousand Oaks, CA 91320-1789 Made in Germany

FP0 2

3 55513 72001 4

LOT
Exp.

1 x 60 mg Single Use Vial
NDC 55513-720-01

AMGEN
prolia
(denosumab)
60 mg/mL

Each vial contains: 60 mg denosumab,
17 mM acetate, sodium hydroxide to a
pH of 5.2, 4.7% sorbitol, Water for
Injection, USP.

Rx Only

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or call 1-877-562-4111.

Single Use Vial

AMGEN
prolia
(denosumab)
60 mg/mL

U.S. Patent Nos. 6,740,522;
7,059,654; 7,364,736; 7,441,060

FPO 1

prolia™
(denosumab)

Next injection date

ONCE
EVERY 6
MONTHS

Go to prolia.com
or call 1-888-PROLIA
to sign up for a free
reminder program.

11/05