

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125320

**RISK ASSESSMENT and RISK
MITIGATION REVIEW(S)**



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: May 19, 2010

To: Scott Monroe, M.D., Director
Division of Reproductive and Urologic Products (DRUP)

Through: Claudia Karwoski, Pharm D, Director
Division of Risk Management (DRISK) *Claudia Karwoski*
Office of Surveillance and Epidemiology (OSE) *5/19/10*

From: Denosumab Risk Management Team

Scientific Lead:
Elizabeth Donohoe, MD, Medical Officer (DRISK/OSE)

Team Members:

- Brian Gordon, MA, Social Science Reviewer (DRISK)
- Kate Heinrich, MA, Health Education Reviewer (DRISK)
- Janice Maniwang, Regulatory Review Officer (DDMAC)
- Suzanne Robottom, Pharm.D., Team Leader (DRISK)

Subject: REMS Final Review

Drug Name(s): Prolia (denosumab)

Submission: Proposed Prolia REMS submission received May 13, 2010 from DRUP

Application Type/Number: BLA 125320

Applicant/sponsor: Amgen

OSE RCM #: 2009-133

1 INTRODUCTION

This review responds to the request by the Division of Reproductive and Urologic Products (DRUP) for the Office of Surveillance and Epidemiology's (OSE) Division of Risk Management (DRISK) to review and comment on the sponsor's proposed Risk Evaluation and Mitigation Strategy (REMS) for denosumab (Prolia); the REMS was received January 25, 2010.

Denosumab has a proposed indication for treatment of post-menopausal osteoporosis. Additional proposed indications include prevention of post-menopausal osteoporosis and treatment and prevention of bone loss associated with hormone ablation therapy in patients with breast or prostate cancer. However, these indications are not approved and not included in this review cycle. Denosumab is a human monoclonal antibody targeting RANK ligand, an important factor in regulation of bone loss. This product is a subcutaneous injection to be given every six months.

The review division sent the sponsor a REMS Notification Letter (dated October 2, 2009) and a CR letter (dated October 16, 2009). The REMS Notification Letter included a requirement that the REMS include a Medication Guide (MG) and a communication plan (CP) to ensure that the benefits of the drug outweigh the risks of serious infection including skin infection, dermatologic adverse events, and over-suppression of bone turnover. The letter also requested a timetable for submission of assessments and information needed for assessments. The CR letter referenced the REMS Notification Letter but did not include any additional REMS-related guidance.

This review primarily addresses the final Prolia REMS submission, received May 13, 2010. The final REMS Document, Dear Healthcare Provider (DHCP) Letter, and REMS-dedicated webpage screenshot are attached to this review.

2 MATERIAL REVIEWED

- Denosumab REMS Notification Letter dated October 2, 2009 (included REMS request).
- Denosumab CR letter dated October 16, 2009.
- Denosumab REMS submission received May 13, 2010 via email from DRUP (REMS and DHCP Letter sent at 11:45 a.m.; REMS-dedicated webpage, REMS link off of the homepage and REMS Supporting Document sent at 2:45 p.m.)
- DRISK interim denosumab REMS reviews dated April 7, 2010, April 30, 2010 and May 12, 2010.
- DRISK review of Proposed Risk Management Plan, dated September 4, 2009.

3 RESULTS OF REVIEW

The Sponsor's proposed REMS includes the following:

3.1 GOALS :

The proposed goals of the REMS are:

- To inform healthcare providers 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.

Review Comment: These Goals are consistent with our interim comments to sponsor.

3.2 PROPOSED REMS ELEMENTS:

The REMS includes a Medication Guide, Communication Plan, and a timetable for submission of assessments of the REMS. Each element of the REMS is described below.

3.2.1 Medication Guide

The Medication Guide will be attached to the final REMS (Appendix 1).

Review Comments: The sponsor proposed a plan to distribute the Medication Guide that appears to be consistent with 21 CFR 208.24. The Medication Guide has been reviewed separately and completed April 8, 2010). Inclusion of a Medication Guide is consistent with the REMS request.

3.2.2 Communication Plan

A. Audience – the sponsor will target endocrinologist, rheumatologist, gynecologist, and primary care physicians who have written at least one prescription for an osteoporosis medication in the last 12 months.

B. Distribution plan

- i. Dear Healthcare Professional Letter. The DHCP letter will be sent within 60 days of approval of the REMS and/or in conjunction with product launch, whichever is sooner. The letter will also be distributed to new prescribers as described in the REMS document.
- ii. Collaboration with Professional Societies. The sponsor will distribute the DHCP letter to relevant societies delineated in the REMS document.
- iii. REMS website. REMS approved communications materials will be made available via a prominent (single click) link on the homepage of the Prolia product website.

The Dear Healthcare Professional letter is attached to the REMS (Appendix 2).

Review Comment: This CP is consistent with the REMS Notification Letter.

3.2.3 Elements to Assure Safe Use

The REMS does not include Elements to Assure Safe Use.

3.2.4 Implementation System

An implementation system is not a required component of a REMS if there are no elements to assure safe use.

3.2.5 Timetable for Submission of Assessments

The sponsor proposes to assess the REMS at 18 months, 3 and 7 years following approval. 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 so that it will be received by the FDA on or before the due date.

Review Comment: This schedule is acceptable.

3.3 REMS ASSESSMENT PLAN

The sponsor will provide the following components as part of their 18 month, 3-year and 7-year assessment reports.

- A. Patients' understanding of the serious risks of Prolia.
- B. An evaluation of healthcare providers' understanding of the serious risks of Prolia, including the risks of serious infections, dermatologic adverse reactions, and suppression of bone turnover.
- C. A summary of spontaneous and solicited adverse events of serious infections, dermatologic adverse reactions, and events possibly related to suppression of bone turnover reporting by healthcare provider (HCP) type.
- D. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
- E. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

Review Comment: This REMS assessment plan outlined in the Supporting Document is consistent with what FDA has requested.

3.4 Survey Protocols

The sponsor has not yet submitted surveys and protocols for HCP and patients. Comments related to patient and provider surveys were provided by J. Duckhorn (DRISK) and forwarded in Interim Review #1, dated April 7, 2010. The Supporting Document notes that the protocol, survey instrument, and methodology will be finalized after the product labeling and educational materials are finalized, and will be provided to the FDA at least 90 days before the surveys are administered.

3 DISCUSSION

The safety profile of denosumab includes specific risks of serious infections, dermatologic adverse events, and over-suppression of bone turnover (including osteonecrosis of the jaw (ONJ) and fracture healing complications). It is important to note the different treatment options for osteoporosis and the different approaches to risk management in use.

Currently on the market for treatment of post-menopausal osteoporosis, there are: a Parathyroid Hormone (PTH) analog, an estrogen agonist/antagonist (SERM), five bisphosphonates, and three calcitonin products. Of the currently approved treatment options, the only product that requires a REMS is Forteo (recombinant human PTH), due to the risk of osteosarcoma. The Forteo REMS was required post-marketing due to “new safety information” with a new indication that expanded the patient population that may use the drug. The Forteo REMS includes a MG and CP. Evista (raloxifene, an estrogen agonist/antagonist) has a MG related to the risk of thromboembolism but the MG was required pre-FDAAA, so there is no REMS requirement. Denosumab shares some risks with the bisphosphonates: hypocalcemia and ONJ. These risks are currently addressed through product labeling for bisphosphonates. Lastly, the calcitonin products address all risks through labeling.

Denosumab provides a new approach to treatment for osteoporosis. It is a New Molecular Entity (NME), a monoclonal antibody, and the first biologic developed for treatment of osteoporosis. The risk of serious infections with the use of denosumab is of considerable concern; other monoclonal antibodies with a risk of serious infection have required a REMS with MG and CP (golimumab, certolizumab pegol). While the ONJ labeling language will be similar to that of the bisphosphonates, the case of ONJ associated with denosumab is particularly concerning because it was the first pre-market case among osteoporosis treatments. All reported cases associated with the bisphosphonates occurred post-marketing. The additional risks of dermatologic adverse events combined with over-suppression of bone turnover and serious infection cumulatively provide significant safety concerns about the use of denosumab. These risks should be communicated to patients and providers. This risk management approach supports a REMS with MG and CP to ensure the benefits of denosumab outweigh the risks.

4 RECOMMENDATION

The Sponsor has appropriately responded to all Agency comments. The Division of Risk Management in the Office of Surveillance and Epidemiology finds the proposed REMS for Prolia (denosumab) acceptable as appended here. DRISK recommends approval of the Prolia REMS submitted on May 13, 2010. DRISK understands that, as the Prolia REMS goes through the clearance process, additional revisions to the REMS and related materials may be required. DRISK will submit an addendum to this review, if needed, based on any future revisions.

Attachment: Prolia REMS Document with Appendices 2 and 3 [DHCP Letter, REMS-dedicated webpage screenshot]

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 endocrinologist, rheumatologist, gynecologist, 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.

Appendix 2

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

PLACEHOLDER FOR LOGO

Denosumab (Amgen) (PFS) Denosumab (Amgen) (PFS)
Denosumab (Amgen) (PFS) Denosumab (Amgen) (PFS)
Denosumab (Amgen) (PFS) Denosumab (Amgen) (PFS)

[BACK TO HOMEPAGE](#)

Prolia™ (denosumab) Risk Evaluation and Mitigation Strategy

A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration to ensure that the benefits of the drug outweigh its risks.

In order for Amgen to communicate certain risks about Prolia™ (denosumab), Amgen has worked with FDA to develop materials to communicate the risks of:

- Serious infections
- Dermatologic adverse reactions
- Suppression of bone turnover

The REMS program is designed to inform the healthcare providers (HCP) and patients about the risks with Prolia™. To learn more about serious risks, read the important safety information provided in this link, including the Medication Guide, and discuss it with your patients.

The goals of the REMS are:

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

Use the links below to access REMS support material

[Prescribing Information >](#) [Medication Guide >](#)

[Dear Healthcare Professional Letter >](#)

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of Drug Evaluation III
Division of Reproductive and Urologic Products

BLA #:	125320/0
Products:	Prolia (denosumab) for subcutaneous injection
SPONSOR:	AMGEN, Inc.
FROM:	George Benson, M.D. <i>GS Benson 10/2/09</i>
DATE:	October 2, 2009

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require the submission of a REMS if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for Prolia (denosumab) to ensure that the benefits of the drug outweigh the risks of serious infection including skin infection, dermatologic adverse events, and over-suppression of bone turnover. In reaching this determination, we considered the following:

- A. The estimated number of patients in the United States who have postmenopausal osteoporosis is 8 million women based on data from the National Osteoporosis Foundation.¹
- B. Postmenopausal osteoporosis is a serious disease that can have significant associated morbidity and mortality. Osteoporosis is responsible for more than 1.5 million fractures annually, including approximately 300,000 hip fractures, 700,000 vertebral fractures, 250,000 wrist fractures, and more than 300,000 fractures at other sites based on estimates from the National Institute of Arthritis and Musculoskeletal and

¹ <http://www.nof.org/osteoporosis/diseasefacts.htm>

Skin Diseases.² The aim of treatment of postmenopausal osteoporosis is to reduce the risk of fractures. The consequences of long-term osteoporosis can include significant disability and death post-fracture.

- C. In the phase 3 trials, Prolia (denosumab) was demonstrated to be effective in reducing the risk of morphometric vertebral fractures, hip fractures, and all clinical fractures in the majority of women studied.
- D. Prolia will be used for treatment of postmenopausal osteoporosis in women. Treatment is expected to continue every six months throughout the patient's lifetime.
- E. The following adverse events were seen in the phase 3 clinical trials of Prolia (denosumab) and are of concern: serious infections, including serious skin infection, dermatologic adverse events, and over-suppression of bone turnover (including osteonecrosis of the jaw and new fractures including fracture healing complications).
- F. Prolia (denosumab) is a new molecular entity.

In accordance with section 505-1 of FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for Prolia (denosumab). FDA has determined that Prolia (denosumab) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Prolia (denosumab). FDA has determined that Prolia (denosumab) is a product for which patient labeling could help reduce the severity of serious adverse effects and has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use, Prolia (denosumab).

The elements of the REMS will be a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS.

² http://www.niams.nih.gov/Health_Info/Bone/Osteoporosis/default.asp



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

STN: BL 125320/0

AMGEN, Inc.
Attention: Edward S. Burd, Ph.D.
Senior Director, Regulatory Affairs
One Amgen Center Drive
Mail Stop 17-2-B
Thousand Oaks, CA 91320-9978

Dear Dr. Burd:

Please refer to your biologics license application (BLA) submitted under Section 351 of the Public Health Service Act for Prolia (denosumab).

We are reviewing your submission and have the following comments, information requests, and notifications of additional requirements. We request a prompt written response in order to continue our evaluation of your application.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Prolia (denosumab) to ensure that the benefits of the drug outweigh the risks of serious infection including skin infection, dermatologic adverse events, and over-suppression of bone turnover.

Your proposed REMS must include the following:

Medication Guide: As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Prolia (denosumab) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Prolia (denosumab). FDA has determined that Prolia (denosumab) is a product for which patient labeling could help prevent serious adverse effects and has serious risks (relative to benefits) of which

patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use, Prolia (denosumab).

Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Prolia (denosumab).

Communication Plan: We have determined that a communication plan targeted to healthcare providers who are likely to prescribe Prolia (denosumab) will support implementation of the elements of your REMS during the first year after the approval date. The communication plan must provide for the dissemination of information about the risks of serious infection including skin infection, dermatologic adverse events, and over-suppression of bone turnover.

The communication plan must include, at minimum, the following:

- A Dear Healthcare Provider Letter. The letter should provide information regarding appropriate patient selection and should include, as an attachment, the approved Prolia (denosumab) label.
- A description of the intended audience for the communication plan, stating specifically the types and specialties of healthcare providers to which the communication plan will be directed, as well as any professional medical associations and societies that will be sent the communication. The intended audience should include all healthcare providers who are likely to prescribe Prolia (denosumab).
- A schedule for when and how the plan's materials are to be distributed to healthcare providers and medical associations.

Timetable for Submission of Assessments: The proposed REMS must include a timetable for submission of assessments that shall be no less frequent than by 18 months, 3 years, and in the 7th year after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. 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. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Your proposed REMS submission should include two parts: a "proposed REMS" and a "REMS supporting document." Attached is a template for the proposed REMS that you should complete with concise, specific information (see Appendix A). Include information in the template that is specific to your proposed REMS for Prolia (denosumab). Additionally, all relevant proposed REMS materials, including educational and communication materials, should be appended to the proposed REMS. Once FDA finds the content acceptable and determines that the application can be approved, we will include these documents as an attachment to the approval letter that includes the REMS. The REMS, once approved, will create enforceable obligations.

The REMS supporting document should be a document explaining the rationale for each of the elements included in the proposed REMS (see Appendix B).

The REMS assessment plan should include but is not limited to the following:

- a. Evaluation of healthcare providers' understanding of the serious risks of Prolia (denosumab), including the risks of serious infection including skin infection, dermatologic adverse events, and over-suppression of bone turnover, and how to select patients who are appropriate for treatment.
- b. Evaluation of patients' understanding of the serious risks of Prolia (denosumab), including the risks of serious infection including skin infection, dermatologic adverse events, and over-suppression of bone turnover.
- c. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.
- d. A report on failures to adhere to Medication Guide distribution and dispensing requirements, and corrective actions taken to address noncompliance.
- e. A summary of all reported serious infection including skin infection, dermatologic adverse events, and events possibly related to over-suppression of bone turnover, with analysis of adverse event reporting by prescriber type (e.g., endocrinologist, rheumatologist, primary care physician), when available.

Before we can continue our evaluation of this BLA, you will need to submit the proposed REMS.

Under 21 CFR 208.24(d), you are responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided. You should submit marked up carton and container labels of all strengths and formulations with the required statement alerting the dispenser to provide the Medication Guide. We recommend the following language dependent upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

- "Dispense the accompanying Medication Guide to each patient." or
- "Dispense the enclosed Medication Guide to each patient."

Prominently identify the proposed REMS submission with the following wording in bold capital letters at the top of the first page of the submission:

**BLA 125320
PROPOSED REMS**

Prominently identify subsequent submissions related to the proposed REMS with the following wording in bold capital letters at the top of the first page of the submission:

**BLA 125320
PROPOSED REMS-AMENDMENT**

If you do not submit electronically, please send 5 copies of your REMS-related submissions.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)).

If this application is approved, we have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the signal of serious risk of serious infection including skin infection, dermatologic adverse events, and over-suppression of bone turnover.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess these signals of serious risks.

Therefore, based on appropriate scientific data, FDA has determined that, if this application is approved, you will be required, pursuant to section 505(o)(3) of the FDCA, to conduct one or more postmarketing studies of Prolia (denosumab) to assess the signal of serious risk of serious infection including skin infection, dermatologic adverse events, and over-suppression of bone turnover. The specific details of this required postmarketing study or studies will be described more fully in an approval letter for this application, if it is approved.

If you have any questions, please contact the Regulatory Project Manager, Celia Peacock, R.D., M.P.H., at (301) 796-4154.

Sincerely,

George Benson 10/2/09

George Benson, M.D.
Deputy Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosures: Appendix A: REMS Template
Appendix B: Supporting Document

APPENDIX A: REMS TEMPLATE

If you are not proposing to include one of the listed elements, include a statement that the element is not necessary.

Application number TRADE NAME (DRUG NAME)

Class of Product as per label

Applicant name

Address

Contact Information

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S):

List the goals and objectives of the REMS.

II. REMS ELEMENTS:

A. Medication Guide or PPI

If a Medication Guide is included in the proposed REMS, include the following:

A Medication Guide will be dispensed with each [drug name] prescription. [Describe in detail how you will comply with 21 CFR 208.24.]

B. Communication Plan

If a Communication Plan is included in the proposed REMS, include the following:

[Applicant] will implement a communication plan to healthcare providers to support implementation of this REMS.

List elements of communication plan. Include a description of the intended audience, including the types and specialties of healthcare providers to which the materials will be directed. Include a schedule for when and how materials will be distributed. Append the printed material and web shots to the REMS Document.

C. Elements To Assure Safe Use

If one or more Elements to Ensure Safe Use are included in the proposed REMS, include the following:

List elements to assure safe use of Section 505-1(f)(3)(A-F) included in this REMS. Elements to assure safe use may, to mitigate a specific serious risk listed in the labeling, require that:

- A. Healthcare providers who prescribe [drug name] have particular training or experience, or are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;
- B. Pharmacies, practitioners, or healthcare settings that dispense [drug name] are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;
- C. [Drug name] may be dispensed to patients only in certain healthcare settings (e.g., hospitals);
- D. [Drug name] may be dispensed to patients with documentation of safe-use conditions;
- E. Each patient using [drug name] is subject to certain monitoring. Append specified procedures to the REMS; or
- F. Each patient using [drug name] be enrolled in a registry. Append any enrollment forms and other related materials to the REMS Document.

D. Implementation System

If an Implementation System is included in the proposed REMS, include the following:

Describe the implementation system to monitor and evaluate implementation for, and work to improve implementation of, Elements to Assure Safe Use (B),(C), and (D), listed above .

E. Timetable for Submission of Assessments

For products approved under an NDA or BLA, specify the timetable for submission of assessments of the REMS. The timetable for submission of assessments shall be no less frequent than by 18 months, 3 years, and in the 7th year after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. 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. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

APPENDIX B: SUPPORTING DOCUMENT

This REMS Supporting Document should include the following listed sections 1 through 6. If you are not proposing to include one of the listed elements, the REMS Supporting Document should simply state that the element is not necessary. Include in section 4 the reason you believe each of the potential elements you are proposing to include in the REMS is necessary to ensure that the benefits of the drug outweigh the risks.

1. Table of Contents
2. Background
3. Goals
4. Supporting Information on Proposed REMS Elements
 - a. Additional Potential Elements
 - i. Medication Guide
 - ii. Patient Package Insert
 - iii. Communication Plan
 - b. Elements to Assure Safe Use, including a statement of how the elements to assure safe use will mitigate the observed safety risk
 - c. Implementation System
 - d. Timetable for Submission of Assessments of the REMS (for products approved under an NDA or BLA)
5. REMS Assessment Plan (for products approved under a NDA or BLA)
6. Other Relevant Information