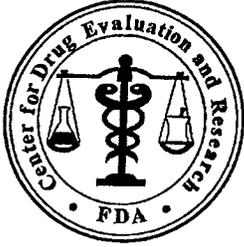


**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125320

OTHER 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, MD, Director
Division of Reproductive and Urology Products

Through: Carlos M Mena-Grillasca, RPh, Team Leader *C Mena 5/19/10*
Denise Toyer, PharmD, Deputy Director *DPT 5/20/2010*
Division of Medication Error Prevention and Analysis

From: Judy Park, PharmD, Safety Evaluator *Judy Park 5/19/10*
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Prolia (Denosumab) Injection
60 mg/mL

Application Type/Number: BLA 125320

Applicant: Amgen

OSE RCM #: 2010-503-1

1 INTRODUCTION

This review is written in response to a request from the Division of Reproductive and Urology Products for a review of the revised Prolia labels and labeling in response to the Division of Medication Error Prevention and Analysis' previous comments to the Applicant. DMEPA reviewed the proposed label and labeling under OSE Reviews # 2009-162 dated September 24, 2009 and #2010-503 dated April 5, 2010.

2 MATERIAL REVIEWED

The Division of Medication Error Prevention and Analysis (DMEPA) used Failure Mode and Effects Analysis¹ (FMEA) to evaluate the revised labels and labeling submitted by the Applicant on May 7, 2010 (Appendix A and B). We also evaluated the recommendations in OSE reviews #2009-162 and #2010-503.

3 CONCLUSION

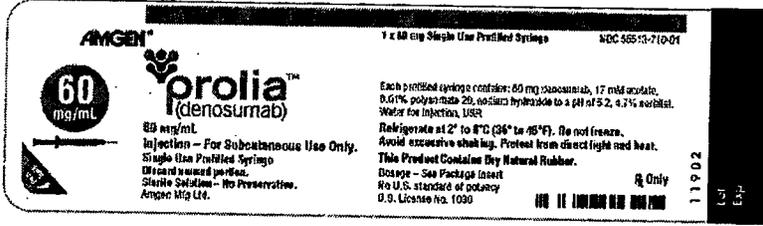
The Applicant has satisfactorily revised the labels and labeling per our previous reviews. They have addressed all of our concern thus, we have no further comments.

If you have questions or need clarifications, please contact Maria Wasilik, OSE Project Manager, at (301) 796-0567.

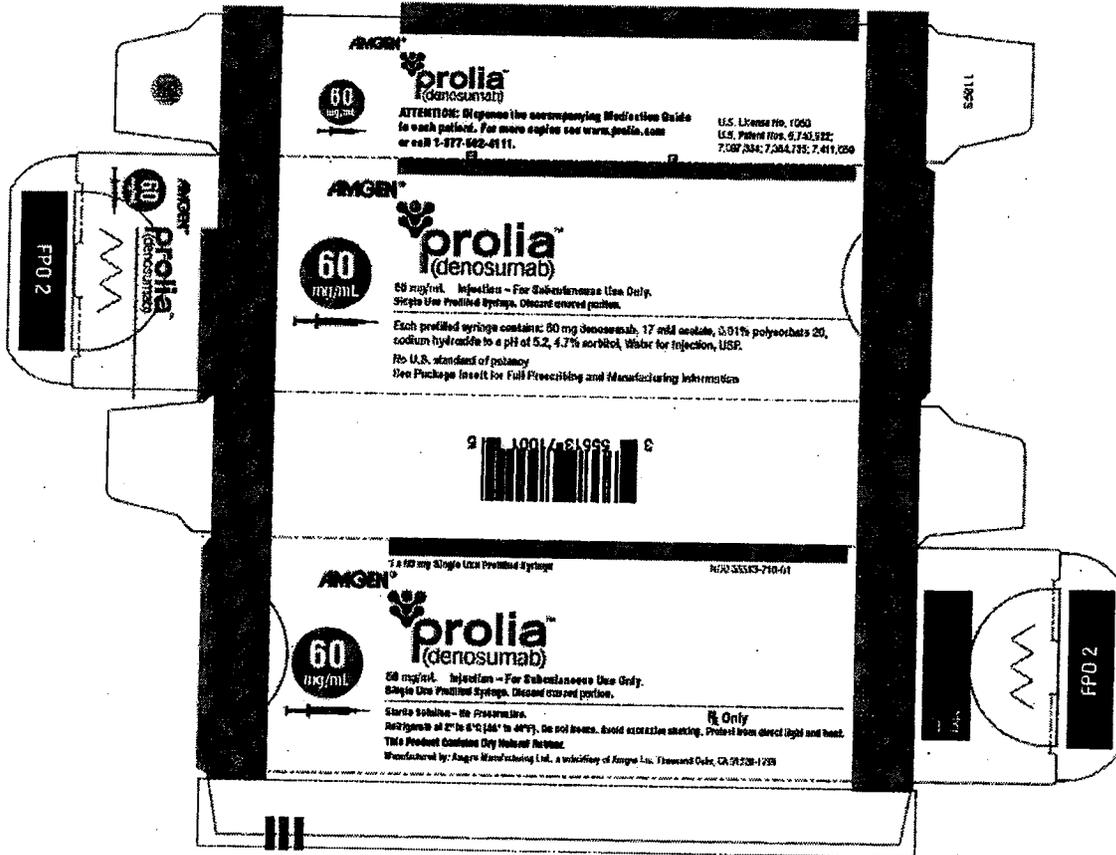
¹ Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

4 APPENDICES

APPENDIX A: Syringe Topweb

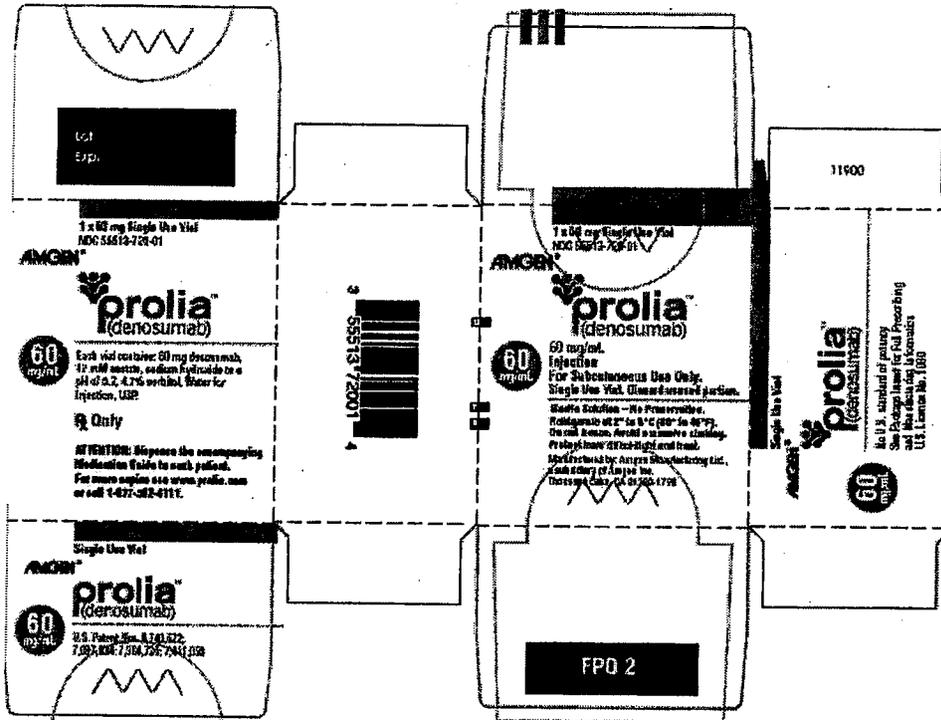


APPENDIX B: Syringe Dispensing Pack



Best Possible Copy

APPENDIX C: Vial Dispensing Pack





Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

**Pediatric and Maternal Health Staff – Maternal Health Team
Addendum to March 16, 2010 Review**

Date: May 7, 2010

From: Jeanine Best, MSN, RN, PNP
Clinical Analyst, Pediatric and Maternal Health Staff

Handwritten signature: Jeanine Best
5/7/10

Through: Karen B. Feibus, M.D.
Medical Team Leader, Pediatric and Maternal Health Staff

Handwritten signature: K. B. Feibus
5/10/2010

Lisa Mathis, MD
OND Associate Director, Pediatric and Maternal Health Staff

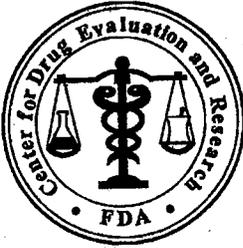
Handwritten signature: Lisa Mathis
5/10/2010

To: Division of Reproductive and Urologic Products (DRUP)

Drug: Denosumab for Subcutaneous Injection, BLA 125320

Subject: Pregnancy Surveillance Program

In a review dated March 16, 2010, the Maternal Health Team (MHT) concluded that a required pregnancy exposure registry was not the appropriate method to collect meaningful data about women who are exposed to denosumab within six months of conception or during pregnancy, as the product does not have currently have an indication for use in women of childbearing potential. Instead, the MHT recommended that Amgen, Inc. use their already developed voluntary Pregnancy Surveillance Program that they established for all of their products. Given that the indicated population for Prolia® (denosumab) will not include women of childbearing potential, this approach is the most feasible and reasonable method to collect denosumab pregnancy exposure data at this time. Amgen concurred with this approach and has included the contact information for their Pregnancy Surveillance Program in the agreed upon Prolia® (denosumab) labeling. No Postmarketing Requirement (PMR) or Postmarketing Commitment (PMC) is necessary at this time to collect pregnancy exposure data. A Pregnancy Exposure Registry should be required as a PMR when Prolia® (denosumab) has an indication approved for use in women of childbearing potential in order to gather meaningful pregnancy outcome data that can be used to better inform labeling.



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: April 8, 2010

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

Through: Claudia Karwoski, Pharm D, Director *Claudia Karwoski 4/8/10*
Division of Risk Management (DRISK)

LaShawn Griffiths, RN, MSHS-PH, BSN *LaShawn Griffiths 4/8/10*
Patient Labeling Reviewer, Acting Team Leader
Division of Risk Management

From: Robin Duer, RN, BSN, MBA *Robin Duer 4/8/10*
Patient Product Labeling Reviewer
Division of Risk Management

Subject: DRISK Review of Patient Labeling (Medication Guide)

Drug Name(s): TRADENAME (denosumab) Injection

BLA # 125320

Applicant/sponsor: Amgen

OSE RCM #: 2010-379

15 pages(s) of Draft Labeling have been Withheld in Full immediately following this page as B4 (CCI/TS)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

*****PRE-DECISIONAL AGENCY INFORMATION*****

Date: April 5, 2010

To: Nenita Crisostomo, Regulatory Health Project Manager
Division of Reproductive and Urology Products (DRUP)

From: Cynthia Collins, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Cc: Janice Maniwang, Regulatory Review Officer (DDMAC)
Sangeeta Vaswani, Group Leader (DDMAC)

Re: **BLA 125320: PROLIA (denosumab)**
DDMAC label consult response: Prolia Medication Guide

Cynthia Collins
04-05-10

DDMAC has reviewed the following draft label materials for Prolia:

- **Medication Guide**
 - document entitled "draft-med-guide-text.FDA edits.doc"
 - last revised by Amgen on February 26, 2010
 - accessed from March 17, 2010, e-mail from Nita Crisostomo

DDMAC comments on the Prescribing Information for Prolia were provided under separate cover on March 18, 2010. Please see the attached pages for the comments on the Prolia Medication Guide.

DDMAC appreciates the opportunity to provide comments on these materials. If you have any questions regarding the consumer directed materials for Prolia, please contact:

- Cynthia Collins
(301) 796-4284
e-mail: cynthia.collins@fda.hhs.gov

4 pages(s) of Draft Labeling have been Withheld in Full immediately following this page as B4 (CCI/TS)



**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: April 5, 2010

To: Scott Monroe, MD, Director
Division of Reproductive and Urology Products

Through: Carlos M Mena-Grillasca, RPh, Team Leader *CMena 4/5/2010*
Denise Toyer, PharmD, Deputy Director *D.Toyer 4/5/2010*
Division of Medication Error Prevention and Analysis

From: Judy Park, PharmD, Safety Evaluator *J.Park 4/5/10*
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Prolia (Denosumab) Injection
60 mg/mL

Application Type/Number: BLA 125320

Applicant: Amgen

OSE RCM #: 2010-503

1 INTRODUCTION

This review is written in response to a request from the Division of Reproductive and Urology Products for a review of the revised Prolia labels and labeling in response to the Division of Medication Error Prevention and Analysis' previous comments to the Applicant. DMEPA reviewed the proposed label and labeling under OSE RCM # 2009-162 dated September 24, 2009.

2 MATERIAL REVIEWED

The Division of Medication Error Prevention and Analysis (DMEPA) used Failure Mode and Effects Analysis¹ (FMEA) to evaluate the revised labels and labeling submitted by the Applicant on March 25, 2010 (Appendix A and B). We also evaluated the recommendations in OSE review #2009-162.

3 CONCLUSION

The Applicant has satisfactorily revised the labels and labeling per our previous review. They have addressed all of our concern thus, we have no further comments.

If you have questions or need clarifications, please contact Maria Wasilik, OSE Project Manager, at (301) 796-0567.

2 pages(s) of Draft Labeling have been Withheld in Full immediately following this page as B4 (CCI/TS)

¹ Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.



Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Federal Research Center
Tel. 301-796-4242

Memorandum

Label Review-Amendment

Application Number: STN 125320/0

Name of Drug: Prolia™ (denosumab)

Sponsor: Amgen, Inc.

Material Reviewed: Prolia™ (denosumab) Labeling

Submission Date: February 23, 2009

OBP Receipt Date: February 23, 2009, March 26, 2010

EXECUTIVE SUMMARY

The carton and container labels for Prolia™ (denosumab) were reviewed and found to comply with the following regulations : 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57 and 21 CFR 200.100. USPC Official 12/1/09-5/1/10, USP 32/NF27. Labeling deficiencies were identified, addressed and mitigated. Please see comments in the conclusions section.

Background:

STN 125320 for denosumab is an original Biologic License Application (BLA) indicated for the treatment and prevention of postmenopausal osteoporosis and bone loss in patients undergoing hormone ablation for prostate or breast cancer. The product is a monoclonal antibody supplied as a sterile, preservative-free, clear, colorless to slightly yellow solution in 60 mg/mL glass vials and in 60 mg/mL pre-filled syringes.

Labels Reviewed: Prolia™ (denosumab) Carton label
Prolia™ (denosumab) Container label
Prolia™ (denosumab) Prescribing Information

Review

I. Container

A. 21 CFR 610.60 Container Label

1. Full label. The following items shall appear on the label affixed to each container of a product capable of bearing a full label:
 - a. The proper name of the product – denosumab – is displayed along with the proprietary name (Prolia). This conforms to the regulation.
 - b. The name, addresses, and license number of the manufacturer – The complete address should be listed, along with the U.S. license number. The manufacturer is listed as Amgen LTD, Thousand Oaks, CA 91320, US License no 1080. This conforms to the regulation.
 - c. The lot number or other lot identification – The lot number is located on the container label. This conforms to the regulation.
 - d. The expiration date – The expiration date is displayed on the container label. This conforms to the regulation.
 - e. The recommended individual dose, for multiple dose containers – This product is supplied in a single use vial and prefilled syringe. A statement appears on the label to this effect. This conforms to the regulation.
 - f. The statement “Rx only” for prescription biologicals – The statement “Rx Only” is located on the label. This conforms to the regulation.
 - g. If a Medication Guide is required under part 208 of the chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label – The container label is too small to display the Medication guide statement. The label is too small to add the statement, so the statement is located on the carton. This conforms to the regulation.

2. **Package label information.** If the container is not enclosed in a package, all the items required for a package label shall appear on the container label. – The container is enclosed in a package (carton). This section does not apply.
 3. **Partial label.** If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label. – This conforms to the regulation.
 4. **No container label.** If the container is incapable of bearing any label, the items required for a container label may be omitted, provided the container is placed in a package which bears all the items required for a package label. – This container bears a label.
 5. **Visual inspection.** When the label has been affixed to the container, a sufficient area of the container shall remain uncovered for its full length or circumference to permit inspection of the contents. The prefilled syringe window for visual inspection is shown in the proposed package insert, however the vial presentation is not shown with any information or reference to the visual inspection – This does not conform to the regulation.
- B. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located on top of the label. The NDC number conforms to 21 CFR 207.35 as a 3-2 Product-Package Code configuration. This conforms to the regulation.
- C. 21 CFR 201.5 Drugs; adequate directions for use – This is not needed for the vial label as the minimum requirements are listed in 21 CFR 610.60.
- D. 21 CFR 201.6 Drugs; misleading statements – The only name that appears on the label is the proprietary and proper name. This conforms to the regulation.
- E. 21 CFR 201.10 Drugs; statement of ingredients – Per 601.2(c)(1), this product is exempt from 610.62 and is regulated by 201.10. The established name, denosumab, is not in parenthesis and does not have the prominence commensurate of the proprietary name, Prolia. This does not conform to the regulation.

- F. 21 CFR 201.15 Drugs; prominence of required label statements – All required statements (“Rx Only”, “Do not freeze”, “Avoid excessive shaking”) are prominent and do not overlap. The statement, “Protect from direct sunlight”, is ambiguous. Seeking clarification from firm. This conforms to the regulation.
- G. 21 CFR 201.17 Drugs; location of expiration date – The expiration date is listed on the label. This conforms to 21 CFR 610.60.
- H. 21 CFR 201.25 Bar code label requirements – Bar code appears on the label. This conforms to the regulation.
- I. 21 CFR 201.50 Statement of identity – The established name (denosumab) is stated on the label. The established name and proprietary name (Prolia) conform to 21 CFR 201.10. This conforms to the regulation.
- J. 21 CFR 201.51 Declaration of net quantity of contents – The net quantity of contents is declared on the label. The containers are marked “Single-Use”. This conforms to the regulation.
- K. 21 CFR 201.55 Statement of dosage – The statement “60 mg/mL” and “Single Use Vial” or “Single use Prefilled Syringe” is displayed on the label. This conforms to the regulation.
- L. 21 CFR 201.100 Prescription drugs for human use – The label bears statements of “Rx Only” and other pertinent information. This conforms to the regulation.

Proposed Labels

(b) (4)



Vial Container Label

(b) (4)



II. Carton

A. 21 CFR 610.61 Carton/Package Label –

- a. The proper name of the product – The proper name (denosumab) and the proprietary name (Prolia) are displayed on the front and back panels of the carton. This conforms to the regulation.
- b. The name, addresses, and license number of the manufacturer. The manufacturer is listed as Amgen LTD, Thousand Oaks, CA 91320, US License no 1080. This conforms to the regulation.
- c. The lot number or other lot identification – The lot number is on the top panel of the carton. This conforms to the regulation.
- d. The expiration date – The expiration date is listed below the lot number on the top panel of the carton. This conforms to the regulation.
- e. The preservative used and its concentration, if no preservative is used and the absence of a preservative is a safety factor, the words “no preservative” –The statement “No Preservative” is displayed on the carton. This conforms to the regulation.
- f. The number of containers, if more than one – There is only one package container per drug. Each package contains one vial of drug or one prefilled syringe and is marked, “Single-use”. This conforms to the regulation.

- g. The amount of product in the container expressed as (1) the number of doses, (2) the volume, (3) units of potency, (4) weight, (5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable – The amount of product is expressed as a concentration of 60 mg/mL per container.
- h. The recommended storage temperature – The statement “Store at 2-8°C (36 to 46°F) is displayed on the front panel of the carton. This conforms to the regulation.
- i. The words “Shake Well”, “Do not Freeze” or the equivalent, as well as other instructions, when indicated by the character of the product – The statements “Protect from direct sunlight”, “Do not freeze”, and “Avoid excessive shaking.” This conforms to the regulation. Clarification of direct sunlight and excessive shaking.
- j. The recommended individual dose if the enclosed container(s) is a multiple-dose container – Only one single-use vial and prefilled syringe in each carton. Therefore, this does not apply.
- k. The route of administration recommended, or reference to such directions in and enclosed circular – The statement “For Subcutaneous Use Only” is located on the front panel of the carton. Suggestion: Consistency of dosage form and package insert:

Prolia
(denosumab)
Injection
For Subcutaneous Use
- l. Known sensitizing substances, or reference to enclosed circular containing appropriate information –none listed. Will ask applicant to supply applicable information.
- m. The type and calculated amount of antibiotics added during manufacture – none listed. This conforms to the regulation.
- n. The inactive ingredients when a safety factor, or reference to enclosed circular containing appropriate information. USPC Official 12/1/09-5/1/10, USP 32/NF27, <1091> Labeling of Inactive Ingredients, the list of all inactive ingredients must be in alphabetical order. - Inactive

ingredients are listed on the back panel of the carton, however the ingredients are not in alphabetical order. This does not conform to the regulations.

- o. The adjuvant, if present –None present. This conforms to the regulation.
 - p. The source of the product when a factor in safe administration – Will ask applicant to provide if applicable.
 - q. The identity of each microorganism used in manufacture, and, where applicable, the production medium and the method of inactivation, or reference to an enclosed circular containing appropriate information. – None used. This conforms to the regulation.
 - r. Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the words “No U.S. standard of potency” – “No U.S. Standard of Potency” is displayed on the carton. This conforms to the regulation.
 - s. The statement “Rx only” for prescription biologicals – The statement “Rx Only” is located on the carton. This conforms to the regulation.
 - t. If a Medication Guide is required under part 208 of this chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label – This does not conform to the regulation.
- B. 21 CFR 610.62 Proper name; package label; legible type [*Note: Per 21 CFR 601.2(c)(1), certain regulation including 21 CFR 610.62 do not apply to the four categories of “specified” biological products listed in 21 CFR 601.2(a)*] – This is an exempted (monoclonal antibody products for in vivo use). Therefore the label does not need to conform to this regulation.
- C. 21 CFR 610.63 Divided manufacturing responsibility to be shown – Amgen Manufacturing Ltd. is the only manufacturer listed on the label. This regulation does not apply.

- D. 21 CFR 610.64 Name and address of distributor
The name and address of the distributor of a product may appear on the label provided that the name, address, and license number of the manufacturer also appears on the label and the name of the distributor is qualified by one of the following phrases: “Manufactured for _____”, “Distributed by _____”, “Manufactured by _____ for _____”, “Manufactured for _____ by _____”, “Distributor: _____”, or “Marketed by _____”. The qualifying phrases may be abbreviated. –no distributor is listed. This regulation does not apply.
- E. 21 CFR 610.65 Products for export – This is for US use only. Therefore, this does not need to conform to the regulation.
- F. 21 CFR 610.67 Bar code label requirements
Biological products must comply with the bar code requirements at §201.25 of this chapter. – Bar code appears on the carton label. This conforms to the regulation.
- G. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located at the top of the front panel of the carton. The NDC number conforms to 21 CFR 207.35 as a 3-2 Product-Package Code configuration. This conforms to the regulation.
- H. 21 CFR 201.5 Drugs; adequate directions for use – The label states “See Package Insert for Full Prescribing Information” This conforms to the regulation.
- I. 21 CFR 201.6 Drugs; misleading statements – The names shown on the carton label are (Prolia) and (denosumab). Therefore, this cannot be confused with other drug, device, food, or cosmetic. This conforms to the regulation.
- J. 21 CFR 201.10 Drugs; statement of ingredients – Per 601.2(c)(1), this product is exempt from 610.62 and is regulated by 201.10. The established name, denosumab, is not in parenthesis and does not have the prominence commensurate of the proprietary name, Prolia. This does not conform to the regulation.
- K. 21 CFR 201.15 Drugs; prominence of required label statements – All required statement (“Rx Only”, “Do not freeze”, “Avoid excessive shaking”) are prominent and do not overlap. The statement, “Protect from direct sunlight”, is ambiguous. This does not conform to the regulation.
- L. 21 CFR 201.17 Drugs; location of expiration date – The expiration date appears under the lot identification number on the carton label. This conforms to 21 CFR 610.60 and 21 CFR 201.17.

- M. 21 CFR 201.25 Bar code label requirements – Bar code appears on the carton label. This conforms to the regulation.
- N. 21 CFR 201.50 Statement of identity – The established name (denosumab) is stated on the label. The established name (denosumab) and proprietary name (trade name) conform to 21 CFR 201.10. This conforms to the regulation.
- O. 21 CFR 201.51 Declaration of net quantity of contents – Net quantity of contents is declared on the carton label. This conforms to the regulation.
- P. 21 CFR 201.55 Statement of dosage – The statement “60 mg/mL” and “Single Use Vial” or “Single use Prefilled Syringe” is displayed on the label. This conforms to the regulation.
- Q. 21 CFR 201.100 Prescription drugs for human use – The label bears statements of “Rx Only” and other pertinent information. This conforms to the regulation.

Proposed Labels



Conclusions and Recommendation:

The following deficiencies were noted in the initial review of the denosumab container and carton labels:

Container

1. Please provide an explanation of visual inspection for the vial configuration to comply with 21 CFR 610.60(e). Information provided and acceptable.
2. Per 21 CFR 208.24(d) and 21 CFR 610.60 (g), include the Medication Guide statement (e.g. Dispense the enclosed Medication Guide to each patient or Dispense accompanying Medication Guide to each patient). If space does not permit, this statement must appear on the carton. Space does not permit, added to the carton label.

Carton

1. Please add applicable agents or a reference to applicable agents to carton labels to comply with 21 CFR 610.61(l) (m) (o) (p) (q). The firm added a reference on the carton, "See Package Insert for Full Prescribing and Manufacturing Information." Acceptable.

2. Inactive ingredients should be listed in alphabetical order per USPC Official 12/1/09-5/1/10, USP 32/NF27, <1091> Labeling of Inactive Ingredients. Information revised and acceptable.

Carton and Container

1. Please provide clarification of the statement, "Protect from direct sunlight" listed on the carton and syringe top label. Information provided and acceptable.
2. Per 21 CFR 601.2(a), denosumab is a "specified" biological product and should follow 21 CFR 201.10 for placement and prominence of the established name and proprietary name. The presentation should include the established name in parenthesis, the dosage form, and the route of administration in close proximity. Consider the following presentation:

**Prolia
(denosumab)
Injection
60 mg/mL
For Subcutaneous Use**

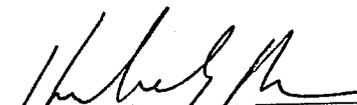
Format suggestion incorporated and acceptable.

Revised Labels submitted March 25, 2010



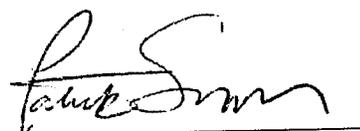
5 pages(s) of Draft Labeling have been Withheld in Full immediately following this page as B4 (CCI/TS)



 5/13/10
Kimberly Rains, Pharm.D.
Regulatory Project Manager
CDER/OPS/OBP

Concurrence:


Sarah Kennett, Ph.D.
Product Reviewer
CDER/OPS/OBP/DMA


Patrick Swann, Ph.D.
Deputy Director
CDER/OPS/OBP/DMA



Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Federal Research Center
Tel. 301-796-4242

Memorandum
Label Review

Application Number: STN 125320/0

Name of Drug: Prolia™ (denosumab)

Sponsor: Amgen, Inc.

Material Reviewed: Prolia™ (denosumab) Labeling

Submission Date: February 23, 2009

OBP Receipt Date: February 23, 2009, March 26, 2010

EXECUTIVE SUMMARY

The carton and container labels for Prolia™ (denosumab) were reviewed and found to comply with the following regulations : 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57 and 21 CFR 200.100. USPC Official 12/1/09-5/1/10, USP 32/NF27. Labeling deficiencies were identified, addressed and mitigated. Please see comments in the conclusions section.

Background:

STN 125320 for denosumab is an original Biologic License Application (BLA) indicated for the treatment and prevention of postmenopausal osteoporosis and bone loss in patients undergoing hormone ablation for prostate or breast cancer. The product is a monoclonal antibody supplied as a sterile, preservative-free, clear, colorless to slightly yellow solution in 60 mg/mL glass vials and in 60 mg/mL pre-filled syringes.

Labels Reviewed: Prolia™ (denosumab) Carton label
Prolia™ (denosumab) Container label

Review

I. Container

A. 21 CFR 610.60 Container Label

1. Full label. The following items shall appear on the label affixed to each container of a product capable of bearing a full label:
 - a. The proper name of the product – denosumab – is displayed along with the proprietary name (Prolia). This conforms to the regulation.
 - b. The name, addresses, and license number of the manufacturer – The complete address should be listed, along with the U.S. license number. The manufacturer is listed as Amgen LTD, Thousand Oaks, CA 91320, US License no 1080. This conforms to the regulation.
 - c. The lot number or other lot identification – The lot number is located on the container label. This conforms to the regulation.
 - d. The expiration date – The expiration date is displayed on the container label. This conforms to the regulation.
 - e. The recommended individual dose, for multiple dose containers – This product is supplied in a single use vial and prefilled syringe. A statement appears on the label to this effect. This conforms to the regulation.
 - f. The statement “Rx only” for prescription biologicals – The statement “Rx Only” is located on the label. This conforms to the regulation.
 - g. If a Medication Guide is required under part 208 of the chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label – The container label is too small to display the Medication guide statement. The label is too small to add the statement, so the statement is located on the carton. This conforms to the regulation.

2. Package label information. If the container is not enclosed in a package, all the items required for a package label shall appear on the container label. – The container is enclosed in a package (carton). This section does not apply.
 3. Partial label. If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label. – This conforms to the regulation.
 4. No container label. If the container is incapable of bearing any label, the items required for a container label may be omitted, provided the container is placed in a package which bears all the items required for a package label. – This container bears a label.
 5. Visual inspection. When the label has been affixed to the container, a sufficient area of the container shall remain uncovered for its full length or circumference to permit inspection of the contents. The prefilled syringe window for visual inspection is shown in the proposed package insert, however the vial presentation is not shown with any information or reference to the visual inspection – This does not conform to the regulation.
- B. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located on top of the label. The NDC number conforms to 21 CFR 207.35 as a 3-2 Product-Package Code configuration. This conforms to the regulation.
- C. 21 CFR 201.5 Drugs; adequate directions for use – This is not needed for the vial label as the minimum requirements are listed in 21 CFR 610.60.
- D. 21 CFR 201.6 Drugs; misleading statements – The only name that appears on the label is the proprietary and proper name. This conforms to the regulation.
- E. 21 CFR 201.10 Drugs; statement of ingredients – Per 601.2(c)(1), this product is exempt from 610.62 and is regulated by 201.10. The established name, denosumab, is not in parenthesis and does not have the prominence commensurate of the proprietary name, Prolia. This does not conform to the regulation.

- F. 21 CFR 201.15 Drugs; prominence of required label statements – All required statements (“Rx Only”, “Do not freeze”, “Avoid excessive shaking”) are prominent and do not overlap. The statement, “Protect from direct sunlight”, is ambiguous. Seeking clarification from firm. This conforms to the regulation.
- G. 21 CFR 201.17 Drugs; location of expiration date – The expiration date is listed on the label. This conforms to 21 CFR 610.60.
- H. 21 CFR 201.25 Bar code label requirements – Bar code appears on the label. This conforms to the regulation.
- I. 21 CFR 201.50 Statement of identity – The established name (denosumab) is stated on the label. The established name and proprietary name (Prolia) conform to 21 CFR 201.10. This conforms to the regulation.
- J. 21 CFR 201.51 Declaration of net quantity of contents – The net quantity of contents is declared on the label. The containers are marked “Single-Use”. This conforms to the regulation.
- K. 21 CFR 201.55 Statement of dosage – The statement “60 mg/mL” and “Single Use Vial” or “Single use Prefilled Syringe” is displayed on the label. This conforms to the regulation.
- L. 21 CFR 201.100 Prescription drugs for human use – The label bears statements of “Rx Only” and other pertinent information. This conforms to the regulation.

II. Carton

A. 21 CFR 610.61 Carton/Package Label –

- a. The proper name of the product – The proper name (denosumab) and the proprietary name (Prolia) are displayed on the front and back panels of the carton. This conforms to the regulation.
- b. The name, addresses, and license number of the manufacturer. The manufacturer is listed as Amgen LTD, Thousand Oaks, CA 91320, US License no 1080. This conforms to the regulation.
- c. The lot number or other lot identification – The lot number is on the top panel of the carton. This conforms to the regulation.
- d. The expiration date – The expiration date is listed below the lot number on the top panel of the carton. This conforms to the regulation.
- e. The preservative used and its concentration, if no preservative is used and the absence of a preservative is a safety factor, the words “no preservative” –The statement “No Preservative” is displayed on the carton. This conforms to the regulation.
- f. The number of containers, if more than one – There is only one package container per drug. Each package contains one vial of drug or one prefilled syringe and is marked, “Single-use”. This conforms to the regulation.

- g. The amount of product in the container expressed as (1) the number of doses, (2) the volume, (3) units of potency, (4) weight, (5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable – The amount of product is expressed as a concentration of 60 mg/mL per container.
- h. The recommended storage temperature – The statement “Store at 2-8°C (36 to 46°F) is displayed on the front panel of the carton. This conforms to the regulation.
- i. The words “Shake Well”, “Do not Freeze” or the equivalent, as well as other instructions, when indicated by the character of the product – The statements “Protect from direct sunlight”, “Do not freeze”, and “Avoid excessive shaking.” This conforms to the regulation. Clarification of direct sunlight and excessive shaking.
- j. The recommended individual dose if the enclosed container(s) is a multiple-dose container – Only one single-use vial and prefilled syringe in each carton. Therefore, this does not apply.
- k. The route of administration recommended, or reference to such directions in and enclosed circular – The statement “For Subcutaneous Use Only” is located on the front panel of the carton. Suggestion: Consistency of dosage form and package insert:
 - Prolia
 - (denosumab)
 - Injection
 - For Subcutaneous Use
- l. Known sensitizing substances, or reference to enclosed circular containing appropriate information –none listed. Will ask applicant to supply applicable information.
- m. The type and calculated amount of antibiotics added during manufacture – none listed. This conforms to the regulation.
- n. The inactive ingredients when a safety factor, or reference to enclosed circular containing appropriate information. USPC Official 12/1/09-5/1/10, USP 32/NF27, <1091> Labeling of Inactive Ingredients, the list of all inactive ingredients must be in alphabetical order. - Inactive

ingredients are listed on the back panel of the carton, however the ingredients are not in alphabetical order. This does not conform to the regulations.

- o. The adjuvant, if present –None present. This conforms to the regulation.
 - p. The source of the product when a factor in safe administration – Will ask applicant to provide if applicable.
 - q. The identity of each microorganism used in manufacture, and, where applicable, the production medium and the method of inactivation, or reference to an enclosed circular containing appropriate information. – None used. This conforms to the regulation.
 - r. Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the words “No U.S. standard of potency” – “No U.S. Standard of Potency” is displayed on the carton. This conforms to the regulation.
 - s. The statement “Rx only” for prescription biologicals – The statement “Rx Only” is located on the carton. This conforms to the regulation.
 - t. If a Medication Guide is required under part 208 of this chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label – This does not conform to the regulation.
- B. 21 CFR 610.62 Proper name; package label; legible type [*Note: Per 21 CFR 601.2(c)(1), certain regulation including 21 CFR 610.62 do not apply to the four categories of “specified” biological products listed in 21 CFR 601.2(a)*] – This is an exempted (monoclonal antibody products for in vivo use). Therefore the label does not need to conform to this regulation.
- C. 21 CFR 610.63 Divided manufacturing responsibility to be shown -- Amgen Manufacturing Ltd. is the only manufacturer listed on the label. This regulation does not apply.

- D. 21 CFR 610.64 Name and address of distributor
The name and address of the distributor of a product may appear on the label provided that the name, address, and license number of the manufacturer also appears on the label and the name of the distributor is qualified by one of the following phrases: "Manufactured for _____".
"Distributed by _____", "Manufactured by _____ for _____",
"Manufactured for _____ by _____", "Distributor: _____", or "Marketed by _____". The qualifying phrases may be abbreviated. –no distributor is listed. This regulation does not apply.
- E. 21 CFR 610.65 Products for export – This is for US use only. Therefore, this does not need to conform to the regulation.
- F. 21 CFR 610.67 Bar code label requirements
Biological products must comply with the bar code requirements at §201.25 of this chapter. – Bar code appears on the carton label. This conforms to the regulation.
- G. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located at the top of the front panel of the carton. The NDC number conforms to 21 CFR 207.35 as a 3-2 Product-Package Code configuration. This conforms to the regulation.
- H. 21 CFR 201.5 Drugs; adequate directions for use – The label states "See Package Insert for Full Prescribing Information" This conforms to the regulation.
- I. 21 CFR 201.6 Drugs; misleading statements – The names shown on the carton label are (Prolia) and (denosumab). Therefore, this cannot be confused with other drug, device, food, or cosmetic. This conforms to the regulation.
- J. 21 CFR 201.10 Drugs; statement of ingredients – Per 601.2(c)(1), this product is exempt from 610.62 and is regulated by 201.10. The established name, denosumab, is not in parenthesis and does not have the prominence commensurate of the proprietary name, Prolia. This does not conform to the regulation.
- K. 21 CFR 201.15 Drugs; prominence of required label statements – All required statement ("Rx Only", "Do not freeze", "Avoid excessive shaking") are prominent and do not overlap. The statement, "Protect from direct sunlight", is ambiguous. This does not conform to the regulation.
- L. 21 CFR 201.17 Drugs; location of expiration date – The expiration date appears under the lot identification number on the carton label. This conforms to 21 CFR 610.60 and 21 CFR 201.17.

- M. 21 CFR 201.25 Bar code label requirements – Bar code appears on the carton label. This conforms to the regulation.
- N. 21 CFR 201.50 Statement of identity – The established name (denosumab) is stated on the label. The established name (denosumab) and proprietary name (trade name) conform to 21 CFR 201.10. This conforms to the regulation.
- O. 21 CFR 201.51 Declaration of net quantity of contents – Net quantity of contents is declared on the carton label. This conforms to the regulation.
- P. 21 CFR 201.55 Statement of dosage – The statement “60 mg/mL” and “Single Use Vial” or “Single use Prefilled Syringe” is displayed on the label. This conforms to the regulation.
- Q. 21 CFR 201.100 Prescription drugs for human use – The label bears statements of “Rx Only” and other pertinent information. This conforms to the regulation.

Proposed Labels

(b) (4)



Conclusions and Recommendation:

The following deficiencies were noted in the initial review of the denosumab container and carton labels:

Container

1. Please provide an explanation of visual inspection for the vial configuration to comply with 21 CFR 610.60(e). Information provided and acceptable.
2. Per 21 CFR 208.24(d) and 21 CFR 610.60 (g), include the Medication Guide statement (e.g. Dispense the enclosed Medication Guide to each patient or Dispense accompanying Medication Guide to each patient). If space does not permit, this statement must appear on the carton. Space does not permit, added to the carton label.

Carton

1. Please add applicable agents or a reference to applicable agents to carton labels to comply with 21 CFR 610.61(l) (m) (o) (p) (q). The firm added a reference on the carton, "See Package Insert for Full Prescribing and Manufacturing Information." Acceptable.

2. Inactive ingredients should be listed in alphabetical order per USPC Official 12/1/09-5/1/10, USP 32/NF27, <1091> Labeling of Inactive Ingredients. Information revised and acceptable.

Carton and Container

1. Please provide clarification of the statement, "Protect from direct sunlight" listed on the carton and syringe top label. Information provided and acceptable.
2. Per 21 CFR 601.2(a), denosumab is a "specified" biological product and should follow 21 CFR 201.10 for placement and prominence of the established name and proprietary name. The presentation should include the established name in parenthesis, the dosage form, and the route of administration in close proximity. Consider the following presentation:

Prolia
(denosumab)
Injection
60 mg/mL
For Subcutaneous Use

Format suggestion incorporated and acceptable.

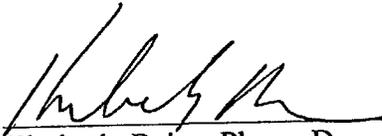
Revised Labels submitted March 25, 2010

Syringe Container label

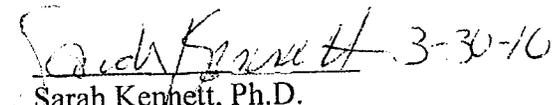


2 pages(s) of Draft Labeling have been Withheld in Full immediately following this page as B4 (CCI/TS)




Kimberly Rains, Pharm.D.
Regulatory Project Manager
CDER/OPS/OBP

Concurrence:

 3-30-10
Sarah Kennett, Ph.D.
Product Reviewer
CDER/OPS/OBP/DMA

 4-6-10
Patrick Swann, Ph.D.
Deputy Director
CDER/OPS/OBP/DMA



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEIII**

FACSIMILE TRANSMITTAL SHEET

DATE: March 19, 2010

To: Edward Burd Senior Manager, Regulatory Affairs	From: Nenita Crisostomo, R.N. Regulatory Health Project Manager
Company: Amgen, Inc.	Division of Reproductive and Urologic Products
Fax number: 805-480-1330	Fax number: 301-796-9897
Phone number: 805-447-3022	Phone number: 301-796-0875

Subject: BLA 125320 Prolia (denosumab) - Package Insert: FDA Recommendations #1

Total no. of pages including cover: 19

Dear Ed,

As promised, attached is the Package Insert containing our recommendations. Please accept all of our changes and delete all of our comments and make your edits on a clean copy, complete with a rationale for each of your changes.

For our immediate review, while enroute for official submission, please provide your response via email to me on or before close of business on March 25, 2010.

If you have any questions, please do not hesitate to contact me.

Best Regards,
Nita

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2130. Thank you.

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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

*****PRE-DECISIONAL AGENCY MEMO*****

Date: March 18, 2010

To: Nenita Crisostomo, RN
Regulatory Project Manager
Division of Reproductive and Urologic Products (DRUP)

From: Janice Maniwang, Pharm.D., M.B.A.  3/18/2010
Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Re: **BLA 125,320**
DDMAC labeling comments for denosumab for Subcutaneous Injection

Background

DDMAC has reviewed the product labeling(PI) for denosumab for Subcutaneous Injection submitted to DDMAC on March 1, 2010.

Please note that our comments are based on the substantially complete version of the draft label sent to DDMAC on March 17, 2010. In addition, we have considered the Forteo PI (approved July 2009) and Reclast PI (approved May 2009) in our review of the draft denosumab PI.

We offer the following comments:

PI

Please see our attached comments.

DDMAC appreciates the opportunity to provide comments on these materials. If you have any questions, please contact:

- Janice Maniwang (Professional directed materials)
(301) 796-3821, or janice.maniwang@fda.hhs.gov

17 pages(s) of Draft Labeling have been Withheld in Full immediately following this page as B4 (CCI/TS)



DEPARTMENT OF HEALTH & HUMAN SERVICES ~~Public Health Service~~

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Pediatric and Maternal Health Staff - Maternal Health Team Review

Date: March 16, 2010 **Date Consulted:** March 2, 2010 *Best 3/16/10*

From: Jeanine Best, MSN, RN, PNP
Clinical Analyst, Pediatric and Maternal Health Staff *Jeanine Best*

Through: Karen B. Feibus, M.D.
Medical Team Leader, Pediatric and Maternal Health Staff *Karen B. Feibus 3/16/10*

Lisa Mathis, MD *LM* 3/16/2010
OND Associate Director, Pediatric and Maternal Health Staff

To: Division of Reproductive and Urologic Products (DRUP)

Drug: Denosumab for Subcutaneous Injection, BLA 125320

Subject: Revised Pregnancy Registry Exposure Protocol, dated January 25, 2010

Consult Request

The Division of Reproductive and Urologic Products (DRUP) consulted the Maternal Health Team to review the draft revised denosumab pregnancy exposure registry protocol submitted to BLA 125320 on January 25, 2010.

INTRODUCTION

AMGEN submitted a Complete Response for Prolia (denosumab) Injection for Subcutaneous Use, BLA 125320, on January 25, 2010, in response to the Agency's October 16, 2009, Complete Response Letter. The current proposed indication under consideration for denosumab is for the treatment of postmenopausal women with osteoporosis at high risk for fracture.

The Maternal Health Team (MHT), of the Pediatric and Maternal Health Staff (PMHS), provided a preliminary review of the Sponsor's draft pregnancy exposure registry (submitted September 8, 2009) on October 9, 2009, but was unable to provide a full review at the time because indications for approval and labeling were not complete. MHT notes that Amgen submitted their draft pregnancy exposure registry voluntarily and not at the request of the Agency.

The Division of Reproductive and Urologic Drug Products (DRUP) consulted MHT on March 2, 2010, to review the revised draft denosumab pregnancy exposure registry.

BACKGROUND

Denosumab

Denosumab is a human monoclonal antibody (IgG2) that inhibits receptor activation of nuclear factor kappa B (RANK) ligand (a TNF-family molecule). RANK ligand (RANKL), also known as osteoprotegerin ligand, is a key regulator (with its receptor RANK) of bone remodeling and essential for the development and activation of osteoclasts. RANKL also regulates T cell/dendritic cell survival and lymph node organogenesis and is involved with the formation of lactating mammary glands in pregnancy.¹ Published reports^{2,3} of reproductive and developmental toxicity studies in pregnant and neonatal mice lacking the RANKL signaling pathway resulted in fetal lymph node agenesis (prenatal exposure) and impaired dentition and bone growth (neonatal exposure). Pregnant mice showed altered maturation of the maternal mammary gland, leading to impaired lactation postpartum. Reproductive and developmental toxicity studies were performed in cynomolgus monkeys; however, maternal dosing occurred only during the period of organogenesis, so the study could not assess the effects of denosumab on later fetal development. In addition, lymph nodes were not examined in the fetal monkeys, even though previous mouse studies demonstrated that signaling via RANKL was necessary for lymph node development. Neither perinatal nor postnatal studies were performed in cynomolgus monkeys.

Pregnancy Exposure Registries

In 2002, FDA published Guidance for Industry on Establishing Pregnancy Exposure Registries. A pregnancy exposure registry is a prospective observational study that actively collects information on a medical product exposure during pregnancy and associated pregnancy outcomes and is one method of collecting data on drug exposure during pregnancy before pregnancy outcomes are known. The main goal of pregnancy exposure registries is to collect

¹ Nakashima T, Wada T, Penninger J. RANKL and RANK as novel therapeutic targets for arthritis. *Curr Opin in Rheumat*, 2003, 15:280-7

² Fata j, Kong, y, Li, j, Sasaki, t, Irie-Sasaki J, Moorehead R, Elliott R, Scully s, Voura E, Lacey D, Boyle, W, Khokha R, Penninger J. The osteoclast differentiation factor osteoprotegerin-ligand is essential for mammary gland development. *Cell*, Sept 2000; 103:41-50

³ Horowitz K, Cupedo T. Development of human lymph nodes and peyer's patches. *Sem in Immune*, 2008, 20:166-70

data about the presence or absence of drug-associated adverse developmental effects when a drug is used during pregnancy. This data is used in labeling to inform clinician and patient decision making. Medical products that are considered good candidates for pregnancy exposure registries include those that have a high likelihood of use by women of childbearing potential. Pregnancy exposure registries are unlikely to be warranted when the product is not used or rarely used by women of childbearing potential.

The decision to establish a pregnancy exposure registry should include consideration of both the need for pregnancy risk information and the feasibility of successfully completing the registry. In order to collect meaningful data, the sample size of a pregnancy exposure registry should be large enough to either detect a difference or show no difference between the exposed and control groups.⁴

Proposed Amgen Pregnancy Registry Exposure Protocol

The revised pregnancy exposure registry protocol (submitted January 25, 2010) states that

(b) (4)

DISCUSSION AND CONCLUSIONS

Amgen presented a well written revised pregnancy exposure registry protocol and agreed to

(b) (4)

MHT does not believe that a postmarketing requirement for a pregnancy exposure registry for denosumab would be the appropriate method to collect pregnancy exposure data at this time for the reasons mentioned above. MHT is aware that Amgen has established a voluntary pregnancy surveillance program that is designed to gather data about pregnancy of women who have had exposure to an Amgen product prior to conception or during pregnancy. The Amgen Pregnancy Surveillance Program and contact information is listed in the labeling of other approved Amgen drug products. This program is voluntary; however, it is another method of collecting drug

⁴ See Guidance for Industry: Establishing Pregnancy Exposure Registries, August 2002

⁵ See Draft Denosumab Pregnancy Exposure Registry Protocol, January 25, 2010

~~exposure data during pregnancy, especially when a prospective observational pregnancy cohort~~ study is not feasible. The Amgen Pregnancy Surveillance Program would be the appropriate method to use at this time to collect data about women who are exposed to denosumab within six months of conception or during pregnancy and should be requested as a postmarketing commitment. MHT has already reviewed the questionnaires used to collect information during pregnancy and on the infant following delivery; however, Amgen should submit their Pregnancy Surveillance Program methodology and materials to BLA 125320, once a postmarketing commitment is agreed upon for this program.

In order to gather meaningful pregnancy outcome data to better inform labeling, a pregnancy exposure registry (prospective observational cohort study) should be required for denosumab if in the future, the product is approved for use in women of childbearing potential. In addition,

(b) (4)

RECOMMENDATIONS

1. MHT recommends against a postmarketing requirement for a pregnancy exposure registry at this time. However, a pregnancy exposure registry should be required once denosumab has an indication approved for use in women of childbearing potential in order to gather meaningful pregnancy outcome data that can be used to better inform labeling.
2. MHT recommends replacing the "Pregnancy Exposure Registry" language in denosumab labeling with "Pregnancy Surveillance Program" language.

3.

(b) (4)

MEMORANDUM

To: Celia Peacock, MPH, RD
Division of Reproductive and Urologic Products

From: Iris Masucci, PharmD, BCPS 
Division of Drug Marketing, Advertising, and Communications
for the Study Endpoints and Label Development (SEALD) Team, OND

Date: December 15, 2009

Re: Comments on draft labeling for denosumab injection
BLA 125320

We have reviewed the proposed label for denosumab (FDA version dated 12/4/09 and received by SEALD on 12/10/09) and offer the following comments. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, labeling Guidances, and FDA recommendations to provide for labeling quality and consistency across review divisions. We recognize that final labeling decisions rest with the Division after a full review of the submitted data.

Please see attached label for recommended changes.

18 pages(s) of Draft Labeling have been Withheld in Full immediately following this page as B4 (CCI/TS)

**Division of Reproductive and Urologic Products
Center for Drug Evaluation and Research**

Date: October 30, 2009

From: Kimberly Hatfield, Ph.D.
Toxicologist

To: BLA 125320 and 125331

Subject: Response to Maternal Health Team labeling consult for BLA 125320 and 125331

The Maternal Health Team (MHT) was consulted on January 22, 2009 to review the Pregnancy and Nursing Mothers section of labeling for Prolia (BLA 125320 and 125331 in DRUP). In a review dated signed and dated on 9-11-2009, the MHT reviewer (Jeanine Best, MSN, RN, PNP) submitted her recommended labeling changes to the BLA based on the Sponsor's proposed label dated 12-19-2008 and revised on 9-4-2009. We acknowledge that many areas of change were useful in improving the label, but have not accepted all changes based on rationale that is provided below. The following is a clean copy of the recommended labeling from MHT, with highlighted areas of comments where we (DRUP) recommend changes. The proposed changes by MHT had also been inadvertently included in draft labeling that was sent to the Sponsor during review, so some of our proposed changes are those suggested by the Sponsor, and are noted as such in our rationale section below.

(b) (4)





Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Maternal Health Team Memorandum

Date: October 9, 2009 **Date Consulted:** September 23, 2009

From: Jeanine Best, MSN, RN, PNP *J. Howard for Jeanine Best 10/14/09*
Clinical Analyst, Pediatric and Maternal Health Staff

Through: Karen B. Feibus, M.D.
Medical Team Leader, Pediatric and Maternal Health Staff *KBF Feibus 10/14/09*

Lisa Mathis, MD *LM 10/14/09*
OND Associate Director, Pediatric and Maternal Health Staff

To: Division of Reproductive and Urologic Products (DRUP)

Drug: Denosumab for Subcutaneous Injection, BLA 125320

Subject: Pregnancy Registry Protocol, dated September 8, 2009

Consult Request

The Division of Reproductive and Urologic Products (DRUP) consulted the Maternal Health Team to review the draft denosumab pregnancy registry protocol submitted to BLA 125320 on September 8, 2009.

Background

AMGEN submitted an original BLA (125320) on December 19, 2008, for Denosumab for Subcutaneous Injection, for the treatment and prevention of osteoporosis in postmenopausal women and for the treatment and prevention of bone loss in patients undergoing hormone ablation for prostate or breast cancer. The application was administratively split for review purposes into BLA 125320 for the treatment and prevention of osteoporosis in postmenopausal women (Division of Reproductive and Urologic Products – DRUP) and BLA 125333 for the treatment and prevention of bone loss in patients undergoing hormone ablation for prostate or breast cancer (Division of Biologic Oncology Products). Amgen submitted a draft pregnancy registry protocol for denosumab on September 8, 2009. DRUP consulted the MHT to review the

draft pregnancy registry protocol. A Complete Response will be issued for denosumab this review cycle, and indications for approval and labeling are not complete at this time.

Additional Background

Denosumab is a human monoclonal antibody (IgG2) that inhibits receptor activator of nuclear factor kappa B (RANK) ligand (a TNF-family molecule). RANK ligand (RANKL), also known as osteoprotegerin ligand, is a key regulator (with its receptor RANK) of bone remodeling and essential for the development and activation of osteoclasts. RANKL also regulates T cell/dendritic cell survival and lymph node organogenesis and is involved with the formation of lactating mammary glands in pregnancy.¹ Published reports^{2,3} of reproductive and developmental toxicity studies in pregnant and neonatal mice lacking the RANKL signaling pathway resulted in fetal lymph node agenesis (prenatal exposure) and impaired dentition and bone growth (neonatal exposure). Pregnant mice showed altered maturation of the maternal mammary gland, leading to impaired lactation postpartum. Reproductive and developmental toxicity studies were performed in cynomolgus monkeys; however, maternal dosing was only done during the period of organogenesis, so the effects of denosumab on later fetal development were not assessed. In addition, lymph nodes were not examined in the fetal monkeys, even though previous mouse studies demonstrated that signaling via RANKL was necessary for lymph node development. Neither perinatal nor postnatal studies were performed in cynomolgus monkeys.

Discussion

MHT is not able to complete a review of the draft denosumab pregnancy registry protocol until indications to be approved are known and labeling is near complete; however, we are able to provide preliminary comments and recommendations. A complete review of the pregnancy registry protocol with additional comments and recommendations will be done when a Complete Response is submitted for denosumab.

(b) (4)

(b) (4)

. Ordinarily, MHT would not have requested pregnancy registry at this time for denosumab because the current proposed denosumab indications do not include females of childbearing potential and complete preclinical embryo-fetal toxicity studies have not been done to support use in females of childbearing potential. MHT acknowledges AMGEN's intent to capture potential pregnancy exposures that may result from off-label use in the clinical setting.

¹ Nakashima T, Wada T, Penninger J. RANKL and RANK as novel therapeutic targets for arthritis. *Curr Opin in Rheumat*, 2003, 15:280-7

² Fata j, Kong, y, Li, j, Sasaki, t, Irie-Sasaki J, Moorehead R, Elliott R, Scully s, Voura E, Lacey D, Boyle, W, Khokha R, Penninger J. The osteoclast differentiation factor osteoprotegerin-ligand is essential for mammary gland development. *Cell*, Sept 2000; 103:41-50

³ Horowitz K, Cupedo T. Development of human lymph nodes and peyer's patches. *Sem in Immune*, 2008, 20:166-70

(b) (4)

Recommendations

Please convey the following denosumab pregnancy registry protocol deficiencies to the Sponsor:

1.  (b) (4)
2.  (b) (4)
3. Resubmit your revised draft denosumab pregnancy registry protocol at the time of your denosumab Complete Response submission.

Please re-consult the revised draft denosumab pregnancy registry protocol to the MHT when it is resubmitted with the Complete Response submission.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 7, 2009

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

FROM: Xikui Chen, Ph.D.
Division of Scientific Investigations

THROUGH: C.T. Viswanathan, Ph.D. *mart: K. Yan 10/7/09*
Associate Director - Bioequivalence
Division of Scientific Investigations

SUBJECT: Review of EIR Covering BLAs 125320 and 125331,
Prolia™ (Denosumab) Injection, 60 mg/mL,
Sponsored by Amgen Inc.

At the request of the DURP, the Division of Scientific Investigations conducted an audit of the clinical portion of the following bioequivalence studies supporting BLAs 125320 and 125331:

Study Number: 20050227

Title: "An Open-Label, Randomized, Single-Dose, Parallel Group Study to Assess the Bioequivalence of Denosumab Lake Center (LC) and Denosumab Thousand Oaks (TO) After a Single Subcutaneous (SC) Injection to Healthy Volunteers"

Study Number: 20060286

Title: "An Open-Label, Randomized, Single-Dose, Parallel Group Study to Assess the Bioequivalence of Denosumab Boehringer Ingelheim Pharma (BIP) and Denosumab Thousand Oaks (ATO) After a Single Subcutaneous (SC) Injection to Healthy Volunteers"

Page 2 - BLAs 125320 and 125331, Prolia™ (Denosumab)
Injection, 60 mg/mL

Study Number: 20050146

Title: "An Open-Label, Randomized, Single-Dose,
Parallel Group Study in Healthy Volunteers
to Assess the Bioequivalence of Denosumab
After Subcutaneous (SC) Administration With
a Pre-filled Syringe (PFS) Versus a
Graduated Syringe"

The clinical portion of study numbers 20050227, 20060286
and 20050146 was conducted at (b) (4)
(b) (4) Following the clinical site
inspection (8/17-31/2009), no Form FDA-483 was issued.

Conclusion:

Following the above inspection, DSI recommends that
clinical data from the audited studies are acceptable for
review.

After you have reviewed this transmittal memo, please
append it to the original BLA submissions.

Xikui Chen, Ph.D.



Final Classification:

(b) (4)

cc:

DSI/Rivera-Lopez/CF

DSI/Viswanathan/Chen/Yau

OND/ODE3/DRUP/Celia Peacock/Theresa Kehoe

OTS/OCP/DCP3/Jang-Ik Lee/Chongwoo Yu

By e-mail:

HER-SW3530/Kara Roden/Diana Guidry

CDER DSI PM TRACK

Draft: XC 10/7/09

Edit: MKY 10/7/09

DSI: (b) (4) O:\BE\EIRCover\125320bio.den.doc

FACTS (b) (4)



**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: October 5 2009

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

Thru: Solomon Iyasu, MD, MPH, Director or
Tarek A. Hammad, MD, PhD, MSc, MS, *Tarek Hammad 10/5*
Associate Director of Epidemiology
Division of Epidemiology (DEPI), Mail Stop 2411

Cynthia J. Kornegay, Ph.D., Team Leader Epidemiologist
Division of Epidemiology (DEPI), Mail Stop 2411 *Cynthia Kornegay*

From: Carolyn A. McCloskey, M.D., M.P.H., Epidemiologist
Division of Epidemiology (DEPI), Mail Stop 2411

Subject: Short Summary of Review of the Proposed Denosumab
Postmarketing Observational Studies (Phase A, methodology and
background rate assessment and Phase B, safety assessment) both
dated 08 September 2009

Drug Name(s): Denosumab (AMG 162)

Application Type/Number: BLA # 125320, 125331

Submission Number:

Applicant/sponsor: Amgen

OSE RCM #: 2009-1714 (Maria Wasilik, OSE PM)

1 INTRODUCTION

The Division of Epidemiology (OSE/DEPI) was consulted by the Division of Reproductive and Urologic Products (DRUP) to review the postmarketing pharmacovigilance studies proposed by Amgen on their BLA product, denosumab, a human IgG₂ monoclonal antibody with osteoclast-suppressing activity indicated for postmenopausal osteoporosis (PMO). Although it was reportedly well-tolerated in clinical trials, there are concerns about potential adverse events (AEs) similar to many of the anti-tumor necrosis factor (TNF) products. DRUP agrees with Amgen's suggestion for a postmarketing pharmacovigilance observational study in four large administrative databases; however, Amgen has refused to consider a surveillance study of the healthcare providers (HCPs) on their experiences with denosumab. DRUP's surveillance suggestion was that HCPs complete a survey on each patient who receives denosumab in their office and follow those denosumab-exposed patients.

DEPI concurs with DRUP in their concerns that although an observational study using administrative databases would provide very helpful information on denosumab, it might be difficult to capture denosumab use and to capture some of the AEs, especially ONJ and atypical fracture, which may be treated outside the healthcare plan. Amgen does propose a comparative analysis within the PMO cohort of denosumab-exposed versus other therapies-exposed AEs (a nested case-control study) but the value of the information from a comparative study depends on a good methodology and validation of the drug use and AE capture. At minimum, DEPI recommends that Amgen identify all postmenopausal women, not just PMO women, for inclusion in the study. DEPI also recommends that the results of Phase A, the development and validation of the methodology and background AE rate assessments, be acceptable to FDA before accepting Phase B, the prospective cohort study, and before approving the product.

An HCP active surveillance study, like a survey of patients receiving denosumab in their office as suggested by DRUP, might better capture denosumab use and it might provide details on possible denosumab-associated AEs that may not be well described in the proposed databases for the observational study. A problem with surveys is the poor response rate. For a survey on only denosumab users, the other problems are the lack of drug use or denominator information and the lack of a good comparator group.

Any safety study proposed for denosumab should include at least 10 years of follow-up.

2 MATERIAL REVIEWED

The following materials were reviewed from Amgen dated 08 September 2009:

1. "Denosumab Global Safety Methodology and Background {AE} Rate Assessment Among Women With Postmenopausal Osteoporosis (PMO) Using Multiple Observational Databases (Denosumab Methodology and Background Assessment [DMBA])" (protocol # 20090521, Phase A)
2. "Denosumab Global Safety Assessment Among Women With Postmenopausal Osteoporosis (PMO) Using Multiple Observational Databases (Denosumab Postmarketing Global Safety Assessment [DPMGSA])" (protocol # 20090522, Phase B)

3 DISCUSSION

Denosumab is a human IgG₂ monoclonal antibody that suppresses osteoclast-mediated bone turnover. It acts like the anti-TNF products, and its proposed indication is for prevention of postmenopausal osteoporosis (PMO).

HCPs will administer denosumab to their patients, most likely after the patient fills their prescription and returns to the HCP's office.

Amgen proposes two postmarketing pharmacovigilance studies. Phase A is a retrospective cohort study on data from 1 January 2005 through 31 December 2009 to identify cohorts of women aged 55 years or older with PMO prior to launch of denosumab and to validate the outcome ascertainment algorithms. Phase A would also identify potential confounding factors (including age, disease severity and other medications, etc.) and selection biases (including medication switches) that might be important in a potential association of denosumab with an AE outcome. Phase B is a prospective cohort study on data from 1 June 2009 through 31 December 2015 (5 year follow up) to compare incidence rates of specified AEs in women with PMO on denosumab with those receiving other osteoporosis therapies and to evaluate new safety signals.

The following AEs of interest are listed in Amgen's proposed protocols:

1. Hypocalcemia – emergency room (ER) or hospitalization
2. Osteonecrosis of the jaw (ONJ)
3. Infections – hospitalizations, especially skin infections
4. Hypersensitivity – ER or hospitalizations (anaphylaxis)
5. Dermatologic events – ER or hospitalization, including Stevens Johnson syndrome, toxic epidermal necrolysis, erythema multiforme
6. Atypical fracture
7. Fracture healing complications
8. New primary malignancies

Amgen proposes to compare PMO women who are denosumab users to the following:

1. PMO women on estrogen
2. PMO women on selective estrogen receptor modulators
3. PMO women on parathyroid hormone (teriparatide)
4. PMO women on branded oral bisphosphonates (alendronate/Fosamax, risedronate/Actonel, ibandronate/Boniva)
5. PMO women on generic bisphosphonates (alendronate, neridronate, olpadronate)
6. PMO women on IV bisphosphonates (ibandronate/Boniva, pamidronate/Aredia, zoledronate/Reclast)
7. PMO women with at least 1 fracture event
8. PMO women with at least 1 switch of therapeutic medication for PMO
9. PMO women who are unable to tolerate bisphosphonates

In addition, 2 other comparisons will be made:

1. Treatment naïve users of denosumab versus other PMO therapies
2. Newly switched to denosumab versus newly switched to other PMO therapies

The proposed observational study will be conducted in the following healthcare data systems:

1. US Medicare (Centers for Medicare & Medicaid Services [CMS]), Parts A, B and D (Enrollees are 65 years old or older; Parts A and B for inpatient and outpatient claims; and Parts B and D for pharmacy data)
2. Kaiser Permanente Medical Care Program, Northern and Southern California (ER, office visit and hospitalization data are captured in their Outpatient and Admission databases; plus access to complete electronic medical records)
3. United HealthCare databases (claims from providers and pharmacies plus laboratory test results and a medical chart review process through a third party vendor provided the patient allows it; however, generic bisphosphonate use may not be identified when the

co-payment is more than the prescription and therefore the pharmacy does not submit a claim)

4. Nordic Country National Health Registry Data Systems (health data on all citizens of Denmark, Finland, Sweden, and Norway) (population-based; data from medical records, hospitalizations, prescriptions, laboratory and pathology results, disease registries, death certificates and socioeconomic data)

The proposed analyses include descriptive statistics, stratified analyses, the use of propensity scores in regression analyses and, for long-term effects, Kaplan-Meier survival curves and Cox proportional hazard regression.

Amgen's proposed protocols are well-researched and thoughtful, both for the claims databases and the comparison of AE incidence in denosumab versus users of other PMO therapies. A major requirement for these studies to be successful, however, will be accurate case ascertainment. Amgen acknowledged several design and methodological challenges to the administrative databases study, specifically: identifying PMO women, identifying and characterizing PMO therapies, identifying possible AEs using ICD-9 codes and algorithms for each database, and the problems of missing data and loss to follow-up. For Phase A, any postmenopausal woman, not just PMO women, should be identified since they may receive denosumab for prevention of osteoporosis; therefore, the background AE rates should be determined for this group as well as the subgroup of PMO women. Phase B should identify and follow all denosumab exposures for AEs, not just PMO women administered denosumab. It may be difficult to identify all denosumab exposures and some of the AEs of interest in administrative databases because denosumab should be administered in the HCP's office and some AEs, such as ONJ and atypical fractures, may require dental records or records of radiographs. Many of these concerns should be addressed by the retrospective database study, Phase A, but this information should be ascertained prior to product approval.

Although the proposed databases may provide valuable information concerning denosumab use and its possible AEs, none of them captures a truly generalizable sample of the US population with accurate and reliable data on a product given in the HCP's office or on the occurrence of the listed AEs of interest in PMO women. Of particular concern would be the AEs that are rare, those that may not be consistently submitted on a claim, and/or those that cannot be identified easily by medical codes (i.e., ICD, CPT, or laboratory). This is not to detract from the important, useful information that may be gleaned from these databases, but to encourage a mechanism to acquire the detailed information needed by DRUP and Amgen in their efforts to accurately label denosumab and to aid in counseling prospective patients through medication guides and communication plans.

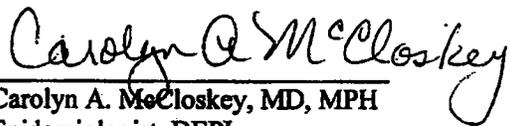
An HCP active surveillance study, like a survey of patients receiving denosumab in their office as suggested by DRUP, might better capture denosumab use and it might provide details on possible denosumab-associated AEs that may not be well described in the proposed databases for the observational study. A problem with surveys is the poor response rate. For a survey on only denosumab users, the other problems are the lack of drug use or denominator information and the lack of a good comparator group.

Any safety study proposed for denosumab should include at least 10 years of follow-up to capture those AEs with long latencies such as ONJ and malignancies.

4 CONCLUSIONS AND RECOMMENDATIONS

DEPI will provide a more in-depth review of the September 8, 2009 protocols, both Phase A & Phase B. In the meantime, the following recommendations cover our main concerns but should not be considered comprehensive:

- DEPI recommends that Amgen pursue the evaluation of the methodologies and background AE rate assessments outlined in their Phase A (protocol # 20090521) but postmenopausal women, with PMO women stratified separately, should be identified as the group most likely to receive denosumab and the background AE rates should be assessed in both groups, with and without PMO. Phase A, revised to include all postmenopausal women, should be completed and reviewed by FDA prior to FDA approval of denosumab.
- Amgen should revise Phase B to identify any denosumab exposure and to follow them. They should plan to conduct Phase B after completion of Phase A and denosumab approval.
- DEPI also recommends that Amgen proceed with designing a study such as a survey of HCPs on their denosumab-exposed patients that will provide them and DRUP with detailed information on denosumab use and possible AEs, especially those AEs presenting challenges to identification in available administrative databases. Amgen should include justification for the sample size and length of follow-up in their proposal and this protocol should be reviewed and accepted by FDA prior to approval of denosumab.
- Finally, DEPI recommends that Amgen extend the follow-up of both the database study and the survey or other study to at least 10 years to capture those AEs with long latencies such as ONJ and malignancies.



Carolyn A. McCloskey, MD, MPH
Epidemiologist, DEPI



**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: September 24, 2009

To: Scott Monroe, MD
Director, Division of Reproductive and Urologic Products
Patricia Keegan, MD
Director, Division of Biologic Oncology Products

Through: Carlos Mena-Grillasca, RPh, Team Leader *C. Mena 9/24/09*
Denise Toyer, PharmD, Deputy Director *D.P. Toyer 9/24/09*
Carol Holquist, RPh, Director *C. Holquist 9/24/09*
Division of Medication Error Prevention and Analysis

From: Judy Park, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Labeling Review

Drug Name(s): Prolia (Denosumab) Injection
60 mg/mL

Application Type/Number: BLA 125320
BLA 125331
BLA 125332
BLA 125333

Applicant: Amgen

OSE RCM #: 2009-162

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1 INTRODUCTION

This review is in response to a January 14, 2009 request from the Division of Reproductive and Urologic Products and the Division of Biologic Oncology Products for an evaluation of the container labels, carton and insert labeling of Prolia to identify areas that could lead to medication errors.

2 METHODS AND MATERIALS

Using Failure Mode and Effects Analysis,¹ the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the container labels and carton labeling submitted on December 19, 2008 and June 12, 2009, and insert labeling submitted on May 4, 2009 to identify vulnerabilities that could lead to medication errors.

3 RECOMMENDATION

Our evaluation noted areas where information on the container labels, carton and insert labeling can be improved to minimize the potential for medication errors. We provide recommendations on the insert labeling Section 3.1, *Comments to the Division*. Section 3.2 *Comments to the Applicant*, contains our recommendations for the container labels and carton labeling. We request the recommendations in Section 3.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact Sandra Griffith, OSE Project Manager for DBOP at 301-796-2445 or Maria Waslik, OSE Project Manager for DRUP at 301-796-2084.

3.1 COMMENTS TO THE DIVISION

A. Insert Labeling

1. Revise the presentation of the drug name, dosage form and route of administration as the following on the first page:

Prolia (denosumab)
Injection
For Subcutaneous Use
2. Delete trailing zeros (e.g. 1.0 mL under *Description* section) and abbreviations (e.g. SC) throughout the labeling. FDA launched a national campaign on June 14, 2006, warning health care providers and consumers not to use error-prone abbreviations, acronyms, or symbols. The abbreviation "SC" and trailing zeros are specifically listed in the ISMP's List of Error-Prone Abbreviations, Symbols and Dose Designation. As part of this campaign, FDA agreed not to approve such abbreviations in the approved labeling.
3. Under *Dosage and Administration, Preparation and Administration* section, clarify if the product must reach room temperature before administration or it can be administered straight out of refrigeration.
4. Under *How Supplied* section, revise the presentation of strength (i.e. 60 mg) as "60 mg/mL."

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3.2 COMMENTS TO THE APPLICANT

A. General Comment for All Labels and Labeling

1. Present the established name so that the active ingredient is in parenthesis and the finished dosage form (e.g. injection) immediately follows the active ingredient as this is the customary presentation of established names.
2. Add the statement "Discard unused portion" immediately following the statement "Single use vial" or "Single use prefilled syringe".

B. Container Label - Syringe

1. If space permits, include the route of administration (i.e. For subcutaneous use) per 21 CFR 200.100(b)(3) to avoid wrong route of administration errors.
2. Relocate the strength so that it immediately follows the established name and dosage form.

C. Carton Labeling – Syringe

1. Remove the line between the drug name and strength so that it does not interfere with the presentation of the drug name, dosage form and strength.
2. Relocate the strength so that it immediately follows the established name and dosage form.
3. Revise the strength unit in the green circle (i.e. 60 mg) to "60 mg/mL."
4. Per 21 CFR 208.24(d), include the Medication Guide statement (e.g. Dispense the enclosed Medication Guide to each patient or Dispense accompanying Medication Guide to each patient).

C. Syringe Topweb Labeling

1. Relocate the strength so that it immediately follows the established name and dosage form.
2. Revise the strength unit in the green circle (i.e. 60 mg) to "60 mg/mL."

D. Container Label – Vial

1. If space permits, include the route of administration (i.e. For subcutaneous use) per 21 CFR 200.100(b)(3) to avoid of wrong route of administration errors.
2. Revise the strength unit in the green circle (i.e. 60 mg) to "60 mg/mL."

E. Carton Labeling – Vial

1. Remove the line between the drug name and strength so that it does not interfere with the presentation of the drug name, dosage form and strength.
2. Revise the strength unit in the green circle (i.e. 60 mg) as "60 mg/mL."
3. Increase the prominence of the route of administration (i.e. For subcutaneous use only) to avoid wrong route of administration errors.
4. Per 21 CFR 208.24(d), include the Medication Guide statement (e.g. Dispense the enclosed Medication Guide to each patient or Dispense accompanying Medication Guide to each patient).

3pages(s) of Draft Labeling have been Withheld in Full immediately following this page as B4 (CCI/TS)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
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Maternal Health Team Review

Date: September, 11, 2009 **Date Consulted:** January 22, 2009 *9/11/09*

From: Jeanine Best, MSN, RN, PNP
Clinical Analyst, Pediatric and Maternal Health Staff *J Best*

Through: Karen B. Feibus, M.D.
Medical Team Leader, Pediatric and Maternal Health Staff *K B Feibus 9/11/09*

Lisa Mathis, M.D. *L Mathis 9/11/09*
OND Associate Director, Pediatric and Maternal Health Staff

To: Division of Biological Oncology Products (DBOP)
Division Reproductive and Urologic Products (DRUP)

Drug: Prolia™ (denosumab) for Subcutaneous Injection

Subject: Pregnancy and Nursing Mothers labeling

Materials Reviewed: Pregnancy and Nursing Mothers subsections of Prolia™
(denosumab) for Subcutaneous Injection labeling, BLAs 125320 and
125333, dated December 19, 2008, and revised by Sponsor
September 4, 2009

Consult Question: Please review the Pregnancy and Nursing Mothers subsections of
Denosumab labeling.

INTRODUCTION

AMGEN submitted an original BLA (125320) on December 19, 2008, for Prolia™ (denosumab) for Subcutaneous Injection, for the treatment and prevention of osteoporosis in postmenopausal women and for the treatment and prevention of bone loss in patients undergoing hormone ablation for prostate or breast cancer. The application was administratively split for review purposes into BLA 125320 for the treatment and prevention of osteoporosis in postmenopausal women (Division of Reproductive and Urologic Products – DRUP) and BLA 125333 for the treatment and prevention of bone loss in patients undergoing hormone ablation for prostate or breast cancer (Division of Biologic Oncology Products).

Denosumab was discussed at an August 13, 2009, Advisory Committee Meeting. Identified safety concerns from clinical trials include serious infections, development of new malignancies, tumor progression with existing malignancies, suppression of bone remodeling, and dermatologic adverse events.¹ Based on these safety concerns the Advisory Committee members recommended approval of denosumab with a Risk Evaluation and Mitigation Strategy (REMS), to ensure the drug benefits outweigh its risks, for treatment of osteoporosis in postmenopausal women and the treatment and prevention of bone loss in patients undergoing hormone ablation for prostate cancer. The Advisory Committee did not recommend approval of denosumab for the prevention of osteoporosis in postmenopausal women or for the treatment and prevention of bone loss in patients undergoing hormone ablation for breast cancer due to the above mentioned safety concerns.

Division of Drug Biologic Products and the Division of Reproductive and Urologic Products consulted MHT to review the pregnancy and Nursing Mothers section of Prolia™ labeling.

BACKGROUND

Denosumab

Denosumab is a human monoclonal antibody (IgG2) that inhibits receptor activator of nuclear factor kappa B (RANK) ligand (a TNF-family molecule). RANK ligand (RANKL), also known as osteoprotegerin ligand, is a key regulator (with its receptor RANK) of bone remodeling and essential for the development and activation of osteoclasts. RANKL also regulates T cell/dendritic cell survival and lymph node organogenesis and is involved with the formation of lactating mammary glands in pregnancy.² Published reports^{3,4} of reproductive and developmental toxicity studies in pregnant and neonatal mice lacking the RANKL signaling pathway resulted in fetal lymph node agenesis (prenatal exposure), and impaired dentition and bone growth (neonatal exposure). Pregnant mice showed altered maturation of the maternal mammary gland, leading to impaired lactation postpartum. Reproductive and developmental toxicity studies were performed in cynomolgus monkeys; however, maternal dosing was only done during the period of organogenesis, so the effects of denosumab on later fetal development were not assessed. In addition, lymph nodes were not examined in the fetal monkeys, even though previous mouse studies demonstrated that signaling via RANKL was necessary for lymph node development. Neither perinatal nor postnatal studies were performed in cynomolgus monkeys. The Pharmacology/Toxicology reviewers from both DRUP and

¹ See FDA Background Document for Meeting of Advisory Committee for Reproductive Health Drugs, July 21, 2009, amended August 3, 2009

² Nakashima T, Wada T, Penninger J. RANKL and RANK as novel therapeutic targets for arthritis. *Curr Opin in Rheumat*, 2003, 15:280-7

³ Fata j, Kong, y, Li, j, Sasaki, t, Irie-Sasaki J, Moorehead R, Elliott R, Scully s, Voura E, Lacey D, Boyle, W, Khokha R, Penninger J. The osteoclast differentiation factor osteoprotegerin-ligand is essential for mammary gland development. *Cell*, Sept 2000; 103:41-50

⁴ Horowitz K, Cupedo T. Development of human lymph nodes and peyer's patches. *Sem in Immune*, 2008, 20:166-70

DBOP determined that the partial reproductive and developmental preclinical studies performed were acceptable for the proposed indicated populations. Complete reproductive and developmental toxicity studies will be required if the denosumab population is expanded to include women of childbearing potential.

Pregnancy and Nursing Mothers Labeling

The Maternal Health Team has been working to develop a more consistent and clinically useful approach to the Pregnancy and Nursing Mothers subsections of labeling. This approach complies with current regulations but incorporates “the spirit” of the Proposed Pregnancy and Lactation Labeling Rule (published on May 29, 2008). The MHT reviewer ensures that the appropriate regulatory language is present and that available information is organized and presented in a clear and useful manner for healthcare practitioners. Animal data in the pregnancy subsection is presented in an organized, logical format that makes it as clinically relevant as possible for prescribers. This includes expressing animal data in terms of species exposed, timing and route of drug administration, dose expressed in terms of human exposure or dose equivalents (with the basis for calculation), and outcomes for dams and offspring. For nursing mothers, when animal data are available, only the presence or absence of drug in milk is considered relevant and presented in the label, not the amount.

This review provides MHT’s suggested revisions to the sponsors proposed Pregnancy and Nursing Mothers subsections of Prolia™ (denosumab) for Sucuntaeous Injection labeling.

SUBMITTED LABELING

Sponsors Proposed Pregnancy and Nursing Mothers Labeling (September 4, 2009 version)



(b) (4)

8.3 Nursing Mothers

It is not known whether [TRADENAME] is excreted into human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from [TRADENAME], a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

CONCLUSIONS

While the Proposed Pregnancy and Lactation Labeling Rule, published May 2008, is in the clearance process, the MHT is structuring the Pregnancy and Nursing Mothers label information in a way that is in the spirit of the Proposed Rule while still complying with current regulations. The goal of this restructuring is to make the pregnancy and lactation sections of labeling a more effective communication tool for clinicians.

The MHT's recommended labeling for denosumab is provided on pages 4-5 of this review. Appendix A of this review also provides a track changes version of labeling

MATERNAL HEALTH TEAM LABELING RECOMMENDATIONS HIGHLIGHTS OF PRESCRIBING INFORMATION



22 pages(s) of Draft Labeling have been Withheld in Full immediately following this page as B4 (CCI/TS)



**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: 04 September 2009

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

Patricia Keegan, M.D., Director
Division of Biologic Oncology Products

Thru: Claudia Karwoski, Pharm. D., Director
Division of Risk Management (DRISK), OSE

From: Elizabeth Donohoe, M.D., Medical Officer, DRISK
Kathryn O'Connell, M.D., PhD, Medical Officer, DRISK

Subject: Review of proposed Risk Management Plan

Drug Name(s): Denosumab [Prolia]

Application Type/Number: BLA 125320, BLA 125331

Applicant/sponsor: Amgen

OSE RCM #: 2009-133

*Mary Kelly, PhD
for
Claudia Karwoski*

~~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 Management Plan (RMP) for denosumab (Prolia). The sponsor submitted a Risk Management Plan (RMP) for BLA 125320, BLA 125331 on December 19, 2008. Additional information related to risk management activities was submitted by the sponsor for the Advisory Committee meeting held August 13, 2009.

BACKGROUND

Denosumab, trade name Prolia, has proposed indications for treatment and prevention of post-menopausal osteoporosis and treatment and prevention of bone loss associated with hormone ablation therapy in patients with breast or prostate cancer. Denosumab is a human monoclonal antibody targeting RANK ligand, an important factor in regulation of bone loss. This product is a subcutaneous injection given every six months. This review does not specifically address the indications related to bone loss in cancer patients as a DRISK consult was only requested from DRUP. The sponsor submitted an RMP with its NDA application which provides the basis for this review.

Post-menopausal osteoporosis is a disease associated with significant morbidity with estimates of over 8 million persons afflicted in the United States. There are a number of treatment options with varied dosing regimens currently on the market for post-menopausal osteoporosis including five bisphosphonates, an estrogen agonist/antagonist, a Parathyroid Hormone analog and three calcitonin products. Denosumab is a New Molecular Entity (NME) and the first biologic developed for treatment of osteoporosis. There are other monoclonal antibodies on the market with serious risks, such as infections, which have warranted issuance of Medication Guides. Denosumab shares some risks with the bisphosphonates: hypocalcemia and osteonecrosis of the jaw (ONJ); these risks are currently addressed through product labeling for bisphosphonates.

The Food and Drug Administration Amendments Act (FDAAA) of 2007 gives the FDA the authority to require the submission of a REMS from a sponsor for a given product if the FDA determines a REMS is warranted. A sponsor may submit a "risk management" plan, but it is not considered a "REMS" unless the FDA determines that a REMS is warranted. Given the early stage of this products application process, the FDA has not yet determined if a REMS is warranted. The review below addresses the format of the submitted information in general but does not imply that the FDA has agreed that this product requires submission of a REMS from the sponsor.

MATERIAL REVIEWED

- Risk Management Plan (RMP) submitted by the sponsor December 19, 2008.
- Background Information for the August 13, 2009 Advisory Committee meeting
 - submitted by sponsor; and
 - submitted by DRUP
- Advisory Committee findings, August 13, 2009

RESULTS OF REVIEW

Sponsor's RMP Submitted December 2008

The sponsor's RMP submitted in December 2008 largely utilizes routine risk minimization activities through product labeling and routine pharmacovigilance (PV). No "REMS" elements are mentioned in the sponsor's RMP.

The sponsor categorizes associated risks as follows [all requiring routine risk minimization in the RMP]:

Identified Risk: hypocalcemia

Potential Risks: infections, hypersensitivity, cataracts in men with prostate cancer

Important Missing (or Limited) Information: pregnant and lactating women, children and potential off-label use.

With the exception of "potential off-label use", all risks would be addressed through language in Prescribing Information [PI]. The sponsor does not plan any "Additional Risk Minimization Activities" for any of the identified risks. The sponsor's RMP focuses on "product information, labeling, health care professional and patient education where appropriate" yet these efforts are not further defined. There are also additional safety concerns identified by the review division which the sponsor does not specifically include in its RMP; these will be addressed in the discussion below.

In addition to routine PV of the aforementioned risks, the sponsor proposes proactive surveillance [explained below] related to fracture healing complications, ONJ, infections, cataracts and use in children.

Sponsor's Background Materials for the AC Meeting

There is minimal variation between the RMP submitted in December 2008 and the RMP the sponsor included in the background materials for the AC. In the slide set for the AC meeting, the sponsor identifies the following:

Risk Minimization [included in "Warnings and Precautions" Highlights in the PI]:

- Hypocalcemia
- Skin infections
- ONJ

Additional Risk Communication: Labeling

- Eczema
- Cataracts [males with prostate cancer]

It is not clear if "labeling" in this category refers just to the PI or to a possible Patient Package Insert or Medication Guide but, as "additional risk minimization activities" are not identified by the sponsor, it is likely the sponsor planned to limit this information to the PI.

The sponsor's Background Materials includes all risk management activities under "Pharmacovigilance Program" as described below:

Pharmacovigilance:

- Routine: utilizing AE reporting, periodic safety reports [PSRs] and periodic safety update reports [PSURs].

- Proactive:
 - Targeted surveillance and focused questionnaires for specific adverse events of interest [hypocalcemia, skin infections leading to hospitalization, infections, fracture healing complications, ONJ, hypersensitivity, immunogenicity, cataracts, cardiovascular, malignancy, potential off-label use for other indications] that are reported in clinical trials and from the postmarketing experience.
 - Use of health care databases to further elucidate the risk and incidence of adverse events of interest which will detect rare events occurring with a frequency as low as 2.5/100,000.
 - Continued monitoring and adjudication of ONJ.
 - A prospective study related to cataracts.
 - A prospective observational pregnancy exposure registry

Ongoing Risk Assessment

- A comprehensive postmarketing pharmacovigilance program including evaluation of ongoing long-term safety studies in post-menopausal osteoporosis [PMO] and hormone ablation therapy [HALT] trials and from the advanced cancer program. Over 8000 patients are currently enrolled with denosumab exposure planned for up to 10 years.

The sponsor states: “The risks associated with denosumab use and the relevant risk minimization and management of events will be discussed under the appropriate sections of the proposed prescribing information”. These “Risk Minimization Activities” include, by risk:

Hypocalcemia: contraindicated for persons with hypocalcemia; monitor patients predisposed to hypocalcemia; recommend calcium and Vitamin D supplementation

Skin Infections Leading to Hospitalization: advise patients to seek prompt medical attention if they develop signs or symptoms of cellulitis

ONJ: advise patients that good oral hygiene should be practiced during treatment

Potential Off-Label Use for Other Indications: recommended use only in approved indications

DISCUSSION

The safety profile of denosumab carries a number of identified risks (described above). In its RMP, the sponsor has proposed addressing these risks largely through “routine risk minimization activities” in the form of the product label [Prescribing Information]. Additional efforts are warranted to communicate these serious risks to patients and prescribers. The sponsor further proposes monitoring a number of these risks through its planned PV activities, which appear adequate. However, not all safety concerns are specifically included in the sponsor’s proposed RMP.

The review division raised specific safety concerns at the AC, including: occurrence of serious infections, development of new malignancies, dermatologic adverse events and possible oversuppression of bone remodeling. It seems that the risks of infection [including skin, ear, urinary tract, endocarditis, infective arthritis and endocarditis] and dermatologic events remain as significant safety concerns. The sponsor’s RMP includes “infections” but focuses on “skin infections (predominantly cellulitis)” as the related adverse reaction. Additional infections, as noted above and identified by the review division, are not further defined.

If the review division decides to approve this drug, these risks should be communicated to patients and prescribers. It appears that these risks may not be well characterized and additional

data needs should be considered through post-marketing requirements [PMR] overseen by the review division. It is DRISK's understanding that a number of PMRs are being considered, including a post-approval surveillance study, which may address these safety concerns.

The risk of development of new malignancies is difficult to characterize since carcinogenicity studies were not done [no animal studies were done as denosumab is not active in rodent] and the question of oversuppression of bone remodeling requires long-term follow-up for better understanding. Additionally, tumor metastases is a concern for the indications related to bone loss and HALT. These risks could also be addressed through PMRs.

The sponsor's RMP appears to limit its communication efforts to Prescribing Information. Under FDAAA, enacted in 2007, the FDA has authority to require a Risk Evaluation and Mitigation Strategies (REMS) program if it is determined that it is necessary for the benefits of the drug to outweigh the risks. Under FDAAA, a Medication Guide may be required if FDA determines that: patient labeling could help prevent serious adverse events; the product has serious risks that could affect the patient's decision to use or continue to use the drug; or patient adherence to directions is crucial to product effectiveness. A Communication Plan may also be warranted to support risk mitigation and may include a letter to healthcare providers.

Given that other monoclonal antibodies have similar serious risk of infection and require MGs, it is reasonable to require a MG informing patients about the risks of denosumab [infections, skin infections, hypocalcemia, and other risks as identified by the review division]. These risks would also be delineated in the labeling. The support of the Advisory Committee for a Communication Plan is also an important factor. Since denosumab is a new Molecular Entity, targeted education to providers through a health care provider letter informing providers of associated risks could be seriously considered.

The Advisory Committee also recommended that the REMS for denosumab include a patient registry. It is not clear what the intent of that "registry" would be, based on discussion at the AC meeting. It appears that the AC recommended collection of patient safety data for use in long-term adverse event monitoring and analyses.

It is DRISK's opinion that use of a patient "registry" as part of a REMS is important when the point of prescribing or dispensing the drug requires specific patient data. It does not appear that either of these two criteria applies to denosumab. Collection of long-term safety information through a post-marketing requirement [PMR] for such a study, however, may be an option the review division may consider.

RECOMMENDATIONS

DRISK recommends that a REMS including a Medication Guide [MG] and Communication Plan [CP] be considered if the review division decides to approve denosumab. The MG and CP, informing patients and prescribers of the serious risks of denosumab, would necessitate a REMS. Further characterization of known risks and additional risks, including occurrence of new malignancies and suppression of bone remodeling, may be addressed in PMR efforts specified by the review division.

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

CLINICAL INSPECTION SUMMARY

DATE: August 27, 2009

TO: Celia Peacock (Hayes), Regulatory Project Manager
Olga Salis, Regulatory Project Manager
Adrienne Rothstein, Clinical Reviewer
Vaishali Popat, M.D., Medical Officer
Division of Anesthesia, Analgesia, and Rheumatology Products

FROM: Roy Blay, Ph.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

BLAs: 125320 and 125331

APPLICANT: Amgen, Incorporated

DRUG: Prolia

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION:

CONSULTATION REQUEST DATE: February 2, 2009

DIVISION ACTION GOAL DATE: August 19, 2009

PDUFA DATE: October 19, 2009

I. BACKGROUND:

The conduct of protocol entitled #AMG 162 20030216, entitled “A Study to Evaluate Denosumab in the Treatment of Postmenopausal Osteoporosis”, also known as the “FREEDOM” study (Fracture REduction Evaluation of Denosumab in Osteoporosis every 6 Months) and Protocol #AMG 162 20010223 entitled “A Randomized, Double-Blind, Placebo-controlled, Multi-dose Phase 2 Study to Determine the Efficacy, Safety and Tolerability of AMG 162 in the Treatment of Postmenopausal Women with Low Bone Mineral Density” was inspected.

The sites of Drs. Lee and Woodson were selected on the basis of relatively large numbers of protocol violations and low numbers of reported adverse events. The sites of Drs. Teglbjaerg and Supronik were selected because of the enrollment of large numbers of subjects and because most of the clinical data for these applications were derived from foreign sites.

As this application was for a New Molecular Entity (NME), additional inspections were scheduled for Amgen, the sponsor, and (b) (4), the contract research organization (CRO) responsible for converting bone scan images into bone density measurements to be used as primary efficacy endpoint data.

The primary efficacy endpoint was the subject incidence of new vertebral fractures based on a “Yes” or “No” determination during the entire 36-month treatment period.

II. RESULTS (by Site):

Name of CI, Sponsor, CRO Location	Protocol #/ # of Subjects/	Inspection Dates	Final Classification
Site 102 Dr. Eric Lee (previously Eugene Boling, MD) Inland Rheumatology Clinical Research Inc. 548 North 13 th Avenue, Suite 306 Upland, CA 91786	20030216/ 35/	6-15 Apr 2009	NAI
Site 016 Grattan C. Woodson III, MD (Atlanta Research Center 2801 North Decatur Road, Suite 370 Decatur, GA 30033	20010223/ 31/	13-17 Apr 2009	VAI
Site 631 Christence Stubbe Teglbjaerg, MD (previously Bente Juel Riis, MD Centre for Clinical and Basic Research (CCBR), Ballerup Byvej 222 Ballerup 2750, Denmark	20030216/ 555/	8-12 Jun 2009	NAI
Site 826 Jerzy Supronik, MD NZOZ Centrum Medyczne Artur Racewicz Jl Pulaskiego 69 Bialystok 15-337, Poland	20030216/ 67/	1-3 Jun 2009	NAI
(Sponsor) Amgen, Incorporated One Amgen Center Drive Thousand Oaks, CA 91320-1799 Contact: Julie Lepin Director, Regulatory Affairs Ph: 805-447-3040 Fax: 805-480-1330	20030216/ and 20010223/	20 Apr-1 May, 2009	Pending: Interim classification: NAI
(CRO)  Phone  Fax 	20010223/	20-24 Jul 09	Pending: Interim classification: NAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field;
EIR has not been received from the field and complete review of EIR is pending.

1. Eric Lee, M.D.

(previously Eugene Boling, M.D.)
Inland Rheumatology Clinical Research Inc.
548 North 13th Avenue, Suite 306
Upland, CA 91786

- a. **What was inspected:** At this site, 24 of the 35 randomized subjects' records were reviewed. Specific records reviewed included, but were not limited to, consent forms, randomization procedures, the primary efficacy endpoint (new vertebral fractures), protocol deviations, concomitant medications, early discontinuations, adverse events, laboratory reports, sponsor and monitor correspondence, and test article accountability.
- b. **General observations/commentary:** Review of the records noted above revealed no significant discrepancies/regulatory violations.
- c. **Assessment of data integrity:** Data appear acceptable in support of the respective application.

2. Grattan C. Woodson III, M.D.

Atlanta Research Center
2801 North Decatur Road, Suite 370
Decatur, GA 30033

- a. **What was inspected:** At this site, 19 of the 31 enrolled subjects' records were reviewed. Records reviewed included, but were not limited to, IRB and monitor correspondence, adverse events, laboratory results, and study drug compliance.

c. **General observations/commentary:**

At the conclusion of the inspection, a Form FDA 483 was issued for an isolated finding. Subject 316114 was dispensed and administered the test article from an incorrect box; however, the subject did receive the correct randomized test article.

- c. **Assessment of data integrity:** The inspectional finding is unlikely to impact data integrity. The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

3. Christence Stubbe Teglbjaerg, M.D.

(previously Bente Juel Riis, M.D.)
Centre for Clinical and Basic Research (CCBR),
Ballerup Byvej 222
Ballerup 2750, Denmark

- a. **What was inspected:** At this site, 121 of the 555 randomized subjects' records were reviewed. Specific records reviewed included, but were not limited to, consent forms,

subject eligibility criteria, randomization procedures, the primary efficacy endpoint (new vertebral fractures), protocol deviations, concomitant medications, early discontinuations, adverse events, laboratory reports, sponsor and monitor correspondence, and test article accountability.

- b. **General observations/commentary:** Review of the records noted above revealed no significant discrepancies/regulatory violations.
- c. **Assessment of data integrity:** Data appear acceptable in support of the respective application.

4. Jerzy Supronik, M.D.
NZOZ Centrum Medyczne Artur
Racewicz
Ul Pulaskiego 69
Bialystok 15-337, Poland

- a. **What was inspected:** At this site, 50 of the 67 enrolled subjects' records were reviewed. Specific records reviewed included, but were not limited to, consent forms, randomization procedures, the primary efficacy endpoint (new vertebral fractures), protocol deviations, concomitant medications, early discontinuations, adverse events, laboratory reports, sponsor and monitor correspondence, and test article accountability.
- b. **General observations/commentary:** Review of the records noted above revealed no significant discrepancies/regulatory violations.
- c. **Assessment of data integrity:** Data appear acceptable in support of the respective application.

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

- a. **What was inspected:** The inspection included review of, but was not limited to, the following: organizational status and assigned responsibilities, monitoring plans, drug batch records, monitor training documentation, and monitoring reports. Select CRFs from each of the four sites for the four investigators noted above were reviewed.
- b. **General observations/commentary:** Review of the records noted above revealed no significant discrepancies/regulatory violations.
- c. **Assessment of data integrity:** Data appear acceptable in support of the respective application.

6. (b) (4)

- a. **What was inspected:** Receipt and review of the EIR for this inspection is pending.
- b. **General observations/commentary:** A Form FDA 483 was not issued for any findings related to Protocol 20010223 (BLA 125320). Any observations/commentary of significance will be forwarded to the revision division as an addendum after receipt and review of the EIR.
- c. **Assessment of data integrity:** Data integrity will be assessed pending receipt and review of the EIR. Any significant issues impacting data reliability will be forwarded to the revision division as an addendum after receipt and review of the EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Receipt and review of the EIR for (b) (4) is pending. An addendum to this clinical inspection summary will be forwarded to the review division should there be any observations of clinical and regulatory significance discovered after reviewing the EIR.

The data generated by the clinical sites of Drs. Woodson, Lee, Teglbjaerg, and Supronik appear acceptable in support of the respective application.

/Roy Blay/
Roy Blay, Ph.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

/Tejashri Purohit-Sheth/
Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

NDA/BLA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

Application Information		
NDA # BLA STN 125320, 125331	NDA Supplement #000 BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: PROLIA (proposed) Established/Proper Name: denosumab Dosage Form: syringe Strengths: 60 mg/mL		
Applicant: Amgen Agent for Applicant (if applicable):		
Date of Application: December 19, 2008 Date of Receipt: December 19, 2008 Date clock started after UN:		
PDUFA Goal Date: October 19, 2009		Action Goal Date (if different):
Filing Date: February 17, 2009 Date of Filing Meeting: January 28, 2009		
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed Indication(s): -125320-Treatment of osteoporosis in postmenopausal women. -125331-Prevention of osteoporosis in postmenopausal women.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>Refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.</i>		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical disease Priority review voucher submitted
Resubmission after withdrawal? <input type="checkbox"/> Resubmission after refuse to file? <input type="checkbox"/>		
Part 3 Combination Product? <input type="checkbox"/>	<input checked="" type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)]	

<input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (if OTC product):	
List referenced IND Number(s): IND 9837	
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Application Integrity Policy	
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ora/compliance_ref/aiplist.html</i> If yes, explain: If yes, has OC/DMPQ been notified of the submission? Comments:	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
User Fees	
Form 3397 (User Fee Cover Sheet) submitted	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
User Fee Status	<input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).</i>	
Exclusivity	

<p>Does another product have orphan exclusivity for the same indication? <i>Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm</i></p> <p>If yes, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES # years requested: <input type="checkbox"/> NO
<p>If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>):</p> <p>Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>	<input checked="" type="checkbox"/> Not applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
505(b)(2) (NDAs/NDA Efficacy Supplements only)	
<p>1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p> <p>2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).</p> <p>3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?</p>	<input checked="" type="checkbox"/> Not applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO

<p><i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i></p>	
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<p>4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? <i>Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm</i></p>		<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO	
<p>If yes, please list below:</p>			
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>			
<p>Format and Content</p>			
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p> <p>Comments:</p>		<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)	
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>			
<p>If electronic submission: <u>paper</u> forms and certifications signed (non-CTD) or <u>electronic</u> forms and certifications signed (scanned or digital signature)(CTD)?</p> <p><i>Forms include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p> <p>Comments:</p>		<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	
<p>If electronic submission, does it follow the eCTD guidance? (http://www.fda.gov/cder/guidance/7087rev.pdf)</p>		<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	
<p>If not, explain (e.g., waiver granted):</p>			

<p>Form 356h: Is a signed form 356h included?</p> <p><i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i></p> <p>Are all establishments and their registration numbers listed on the form?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Index: Does the submission contain an accurate comprehensive index?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:</p> <p><input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Controlled substance/Product with abuse potential:</p> <p>Abuse Liability Assessment, including a proposal for scheduling, submitted?</p> <p>Consult sent to the Controlled Substance Staff?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>BLAs/BLA efficacy supplements only:</p> <p>Companion application received if a shared or divided manufacturing arrangement?</p> <p>If yes, BLA #</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
Patent Information (NDAs/NDA efficacy supplements only)	
<p>Patent information submitted on form FDA 3542a?</p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
Debarment Certification	
<p>Correctly worded Debarment Certification with authorized signature?</p> <p><i>If foreign applicant, both the applicant and the U.S. Agent must sign the certification.</i></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p> <p>Comments:</p>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	
<p>Field Copy Certification: that it is a true copy of the CMC technical section (<i>applies to paper submissions only</i>)</p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<p><input checked="" type="checkbox"/> Not Applicable (<i>electronic submission or no CMC technical section</i>)</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
Financial Disclosure	
<p>Financial Disclosure forms included with authorized signature?</p> <p><i>Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
Pediatrics	
<p>PREA</p>	
<p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	
<p>Are the required pediatric assessment studies or a full waiver of pediatric studies included?</p> <p>If no, is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included?</p> <ul style="list-style-type: none"> • <i>If no, request in 74-day letter.</i> • If yes, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>

BPCA (NDAs/NDA efficacy supplements only):	
Is this submission a complete response to a pediatric Written Request? <i>If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).</i>	<input type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
Prescription Labeling	
Check all types of labeling submitted. Comments: Additional information has been requested for a PPI, carton labeling and the blister card.	<input type="checkbox"/> Not applicable <input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use <input checked="" type="checkbox"/> MedGuide <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)
Is electronic Content of Labeling submitted in SPL format? <i>If no, request in 74-day letter.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
Package insert (PI) submitted in PLR format? If no , was a waiver or deferral requested before the application was received or in the submission? If before , what is the status of the request? <i>If no, request in 74-day letter.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
MedGuide or PPI (plus PI) consulted to OSE/DRISK? (<i>send WORD version if available</i>)	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES – Med Guide only <input type="checkbox"/> NO
Comments:	
REMS consulted to OSE/DRISK?	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP?	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

Comments:	
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OTC Labeling	
<p>Check all types of labeling submitted.</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)
<p>Is electronic content of labeling submitted?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Are annotated specifications submitted for all stock keeping units (SKUs)?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>If representative labeling is submitted, are all represented SKUs defined?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP?</p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
Meeting Minutes/SPA Agreements	
<p>End-of Phase 2 meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO
<p>Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p>Comments: A meeting request was requested and granted by the Division. After receiving the preliminary comments the sponsor canceled the meeting.</p>	<input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO
<p>Any Special Protocol Assessment (SPA) agreements?</p> <p><i>If yes, distribute letter and/or relevant minutes before filing meeting.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 28, 2009

BLA #: 125320, 125331

PROPRIETARY/ESTABLISHED NAMES: denosumab

APPLICANT: Amgen

BACKGROUND:

Denosumab is a fully human IgG2 monoclonal antibody that inhibits receptor activator of nuclear factor kappa B(RANK) ligand, for the treatment and prevention of osteoporosis in postmenopausal women and for the treatment and prevention of bone loss in patients undergoing hormone ablation for prostate or breast cancer. The proposed proprietary name for denosumab in these indications is PROLIA.

Denosumab drug product is supplied as a single-use, sterile, preservative-free solution intended for delivery by subcutaneous injection, supplied in either a 60 mg/mL prefilled syringe (PFS) or 60 mg/mL vial presentation with a 1.0 mL deliverable volume to support dosing of 60 mg every 6 months (Q6M).

BLA was submitted to the Division on December 30, 2008, as an electronic BLA.

There are 4 indications contained in this BLA. They are as follows:

- The biologic product (denosumab) is not approved.
- Two indications (Treatment of osteoporosis in post-menopausal women and Prevention of osteoporosis in post-menopausal women) will be reviewed in the Division of Reproductive and Urologic (DRUP) Products.
- Two indications (Treatment and prevention of bone loss associated with hormone ablation therapy in patients with prostate cancer and the Treatment and prevention of bone loss associated with hormone ablation therapy in patients with breast cancer) will be reviewed by the Division of Biologic Oncology Products (DBOP).
- Because it is not approved, the indications had to be split out into 4 different STNs (i.e., 4 separate BLAs):

125320/0-Treatment of osteoporosis in postmenopausal women.

125331/0 -Prevention of osteoporosis in postmenopausal women.

125332/0 -Treatment and **prevention** of bone loss associated with hormone ablation therapy in patients with breast cancer.

125333/0 -Treatment and **prevention** of bone loss associated with hormone ablation therapy in patients with prostate cancer.

- Once one indication is approved, the rest will revert to supplements.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Celia Peacock	Y
	CPMS/TL:	Margaret Kober	Y
Cross-Discipline Team Leader (CDTL)	Theresa Kehoe		Y
Clinical	Reviewer:	Vaishali Popat	Y
	TL:	Theresa Kehoe	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OSE	Reviewer:	Sandra Griffin	Y
	TL:		Y
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Chongwoo Yu	Y
	TL:	Myong-Jin Kim	Y
Biostatistics	Reviewer:	Sonia Castillo	Y
	TL:	Mahboob Sobhan	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Kimberly Hatfield	Y
	TL:	Lynnda Reid	Y
Statistics, carcinogenicity	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Sarah Kennett	Y
	TL:	Chana Fuchs	Y
Facility (<i>for BLAs/BLA supplements</i>)	Reviewer:	Patricia Hughes	
	TL:		
Microbiology, sterility (<i>for NDAs/NDA efficacy supplements</i>)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:	John Lee	
	TL:		
Other reviewers	Janice Maniwang (DDMAC)		Y

OTHER ATTENDEES:

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

George Benson, Dep. Director DRUP

See Minutes for other attendees.

505(b)(2) filing issues?	<input checked="" type="checkbox"/> Not Applicable
If yes, list issues:	<input type="checkbox"/> YES
	<input type="checkbox"/> NO
Per reviewers, are all parts in English or English translation?	<input checked="" type="checkbox"/> YES
	<input type="checkbox"/> NO

If no, explain:	
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<p>Electronic Submission comments</p> <p>List comments:</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments:</p> <p>If no, for an original NME or BLA application, include the reason. For example:</p> <ul style="list-style-type: none"> ○ this drug/biologic is not the first in its class ○ the clinical study design was acceptable ○ the application did not raise significant safety or efficacy issues ○ the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease 	<input checked="" type="checkbox"/> YES Date if known: <input type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter

<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Establishment(s) ready for inspection? Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Sterile product? <p>If yes, was Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO

Comments:	<input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
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REGULATORY PROJECT MANAGEMENT

Signatory Authority: Julie Beitz, M.D.

GRMP Timeline Milestones:
10/19/09 PDUFA Action Date

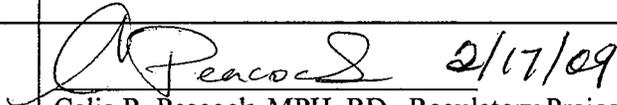
Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

<input checked="" type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review

ACTIONS ITEMS

<input checked="" type="checkbox"/>	Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.
<input type="checkbox"/>	If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input checked="" type="checkbox"/>	If BLA or priority review NDA, send 60-day letter.
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74


 Celia R. Peacock, MPH, RD. Regulatory Project Manager

 Margaret Kober, R.Ph., M.P.A., Chief, Project Management Staff

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Biologic Oncology Products

Application Numbers:

STN: BL 125320/0

STN: BL 125331/0

STN: BL 125332/0

STN: BL 125333/0

Name of Drug: Denosumab

Applicant: Amgen, Incorporated

Material Reviewed:

Submission Date(s): December 19, 2008

Receipt Date(s): December 19, 2008

Submission Date of Structure Product Labeling (SPL): December 19, 2008

Type of Labeling Reviewed: WORD

Background and Summary

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review

The following issues/deficiencies have been identified in your proposed labeling.

General Comments:

1. Include a Boxed Warnings section in the Highlights, Full Prescribing Information (FPI): Contents, and FPI sections of the label to include warnings regarding osteonecrosis, infection and hypocalcemia adverse reactions. Please reference the following: *Draft Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed*

*Warning Section of Labeling for Human Prescription Drug and Biological Products-
Content and Format found at <http://www.fda.gov/CBER/gdlns/boxwarlb.htm>.*

2. Use "active voice" throughout the label.

Highlights:

3. Delete the white space between the major headings and the text underneath.
4. Do not use "TM" after the drug names in Highlights or Table of Contents. Use "TM" only once in the content of labeling (FPI).
5. For biologic products, the dosage form and route of administration are not part of the product name. Relocate the dosage form and route of administration to the next line below.
6. Please revise the DOSAGE AND ADMINISTRATION section, to say "Administer 60 mg every 6 months as a subcutaneous (SC) injection."
7. Rephrase sentence in the DOSAGE FORMS AND STRENGTHS section to read "Single use prefilled syringe containing 60 mg in a 1 mL solution," and "Single use vial containing 60 mg in a 1 mL solution."
8. Include "Skin Infections," and "Hypocalcemia," in the WARNINGS AND PRECAUTIONS section
9. In the USE IN SPECIFIC POPULATION, add the headers "Pregnancy," and "Pediatric Use," and "Renal Impairment" and one of the following statements, as appropriate: "Based on animal data, may cause fetal harm," or "No human or animal data. Use only if clearly needed." (b) (4)

10. Add "Revised [Month/Year]" as the last item in Highlights. [Note: For this new BLA, the revision date will be the month /year that the application is approved].

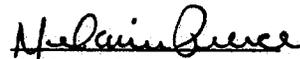
Full Prescribing Information (FPI):

11. Revise the ADVERSE REACTIONS; Section 6.2 Immunogenicity, to include the following standard verbatim statement.

 (b) (4)

12. **USE IN SPECIFIC POPULATIONS: 8.1 Pregnancy:** the labeling must include the appropriate required regulatory statement for Pregnancy Category C. Refer to 21 CFR 201.57(c)(9)(i)(A)(3).
13. **USE IN SPECIFIC POPULATIONS: 8.3 Nursing Mothers:** If a drug is absorbed systemically and is known to be excreted in human milk or excretion in human milk is unknown, this subsection must describe if the drug is associated with serious adverse reactions or has known tumorigenic potential and include required statements, as appropriate. Reference [21 CFR 201.57(C)(9)(iii)].

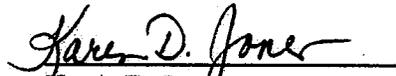
Please address the identified deficiencies/issues and re-submit labeling by (April 3, 2009). This updated version of labeling will be used for further labeling discussions.



Melanie Pierce

Regulatory Health Project Manager

Supervisory Comment/Concurrence:



Karen D. Jones

Chief, Project Management Staff

Drafted: Melanie Pierce/2.23.09

Revised/Initialed: 3.02.09 and 3.03.09

Finalized: 3.03.09

Filename: CSO Labeling Review Template (updated 1-16-07).doc

CSO LABELING REVIEW OF PLR FORMAT

DMPQ

Regulatory Filing Review Memo for BLAs and Supplements

The filing review should seek to identify all omissions of clearly necessary information such as information required under the statute or regulations or omissions or inadequacies so severe that a meaningful review cannot be accomplished. CDER may refuse to file (RTF) an application or supplement as provided by 21 CFR 601.2, and 21 CFR 314.101, including those reasons consistent with the published RTF policy (<http://www.fda.gov/cber/regsopp/8404.htm>). An RTF decision may also be appropriate if the agency cannot complete review of the application without significant delay while major repair or augmentation of data is being done. To be a basis for RTF, the omissions or inadequacies should be obvious, at least once identified, and not a matter of interpretation or judgement about the meaning of data submitted. Decisions based on judgments of the scientific or medical merits of the application would not generally serve as bases for RTF unless the underlying deficiencies were identified and clearly communicated to the applicant prior to submitting a license application, e.g., during the review of the IND or during pre-BLA communications. The attached worksheets, which are intended to facilitate the filing review, are largely based upon the published RTF policy and guidance documents on the ICH Common Technical Document (CTD) (see <http://www.fda.gov/cber/ich/ichguid.htm>).

Where an application contains more than one indication for use, it may be complete and potentially approvable for one indication, but inadequate for one or more additional indications. The agency may accept for filing those parts of the application that are complete for a particular indication, but refuse to file those parts of the application that are obviously incomplete for other indications. You cannot have multiple indications under supplement submissions. If the sponsor submits multiple indications under a supplement, you must unbundle the submission.

CDER management may, for particularly critical biological products, elect not to use the RTF procedure, even where it can be invoked, if it believes that initiating the full review at the earliest possible time will better advance the public health.

STN: 125320/0; 125331/0; 125332/0; 125333/0 Product: Denosumab Applicant: Amgen, Inc.

Final Review Designation (circle one): Standard Priority

Submission Format (circle all that apply): Paper Electronic Combination

Submission organization (circle one): Traditional CTD

Filing Meeting: Date _____ Committee Recommendation (circle one): File RTF

RPM: _____
(signature/date)

Attachments:

- Discipline worksheets (identify the number of lists attached for each part and fill-in the name of the reviewer responsible for each attached list):
 - ____ Part A – RPM
 - X Part B – Product/CMC/Facility Reviewer(s): Maan Abduldayem, Donald Obenhuber, Kalavati Suvarna, Bo Chi
 - ____ Part C – Non-Clinical Pharmacology/Toxicology Reviewer(s): _____
 - ____ Part D – Clinical (including Pharmacology, Efficacy, Safety, and Statistical) Reviewers _____
- Memo of Filing Meeting

PMR/PMC Development Template – ~~PMR #1~~

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

PMR/PMC Description: A retrospective cohort study using multiple existing observational databases to collect data from a 5-year period prior to the availability of denosumab. The study should identify women with postmenopausal osteoporosis and determine the occurrence of serious infection including skin infection, dermatologic adverse events, and over-suppression of bone turnover in each database in order to assess the background rates of those adverse events.

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	<u>January 2010</u>
Study/Clinical trial Completion Date:	<u>May 2011</u>
Final Report Submission Date:	<u>August 2011</u>
Other:	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

This study will assess the background rates of the adverse events of special interest (serious infection including skin infection, dermatologic adverse events, and over-suppression of bone turnover). It is only feasible to conduct this study post-approval. The data obtained in this study will be used to inform the implementation of postmarketing requirement #2.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of this study is to assess the background rates of serious infection including skin infection, dermatologic adverse events, and over-suppression of bone turnover. The data collected will assist in implementation of the long-term observational study (PMR #2). Both studies will assess the signals of the serious risks of serious infection including skin infection, dermatologic adverse events, and over-suppression of bone turnover.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Retrospective cohort study using observational databases
--

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

/Audrey Gassman, M.D./

Deputy Director for Safety, Division of Reproductive and Urologic Products

(signature line for BLAs)

3. If the study/clinical trial is a ~~PMR~~, check the applicable regulation.
If not a PMR, skip to 4.

- Which regulation?

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This is a long-term observational study in administrative databases

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

/Audrey Gassman, M.D./

Deputy Director for Safety, Division of Reproductive and Urologic Products

(signature line for BLAs)

3. If the study/clinical trial is a PMR, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This is a long-term surveillance study.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

/Audrey Gassman, M.D./

Deputy Director for Safety, Division of Reproductive and Urologic Products

(signature line for BLAs)

3. If the study/clinical trial is a PMR, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This PMR is a clinical drug interaction study in postmenopausal women with a CYP3A4 substrate

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

/Audrey Gassman, M.D./

Deputy Director for Safety, Division of Reproductive and Urologic Products

(signature line for BLAs)

3. If the study/clinical trial is a PMR, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Post-approval study to validate new SE-HPLC method.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

/Audrey Gassman, M.D./

Deputy Director for Safety, Division of Reproductive and Urologic Products

(signature line for BLAs)



PMR/PMC Development Template – PMC #6

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

PMR/PMC Description: To submit proposed revisions to the breakloose and extrusion release and shelf-life specifications for pre-filled syringe drug product based on an appropriate statistical method after 15 commercial manufacturing runs.

PMR/PMC Schedule Milestones: Final protocol Submission Date:
Study/Clinical trial Completion Date:
Final Report Submission Date: September 2010
Other:

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The study will be based on an appropriate statistical method after 15 commercial manufacturing runs. Only feasible to conduct post-approval.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Study is to evaluate revisions to breakloose and extrusion release and shelf-life specifications for pre-filled syringe drug product.

3. If the study/clinical trial is a PMR, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Post-approval study to support changes to the breakloose and extrusion release and shelf-life specifications.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

/Audrey Gassman, M.D./

Deputy Director for Safety, Division of Reproductive and Urologic Products

(signature line for BLAs)

PMR/PMC Development Template – PMC #7

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

PMR/PMC Description: To submit proposed revisions to the breakloose and extrusion release and shelf-life specifications for pre-filled syringe drug product based on an appropriate statistical method to reflect increased manufacturing experience.

PMR/PMC Schedule Milestones: Final protocol Submission Date:
Study/Clinical trial Completion Date:
Final Report Submission Date: March 2012
Other:

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The study will be based on an appropriate statistical method after increased manufacturing experience. Only feasible to conduct post-approval.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Study to evaluate proposed revisions to the breakloose and extrusion release and shelf-life specifications for the pre-filled drug product.

3. If the study/clinical trial is a PMR, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Post-approval study to support changes to the breakloose and extrusion release and shelf-life specifications reflecting increased manufacturing experience.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

/Audrey Gassman, M.D./

Deputy Director for Safety, Division of Reproductive and Urologic Products

(signature line for BLAs)