CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125320

PROPRIETARY NAME 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:	March 25, 2010
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 Cmena 3/25/2010 Denise Toyer, PharmD, Deputy Director D.A. Toyer 3/26/2010 Division of Medication Error Prevention and Analysis
From:	Judy Park, PharmD, Safety Evaluator Judy Park 3/25/10 Division of Medication Error Prevention and Analysis
Subject:	Proprietary Name Review
Drug Name(s):	Prolia (Denosumab) Solution for Subcutaneous Injection 60 mg/mL
Application Type/Number:	BLA 125320 BLA 125331 BLA 125332 BLA 125333
Applicant:	Amgen
OSE RCM #:	2010-497

CONTENTS

1 INTRODUCTION

This review is written in response to the anticipated approval of this BLA within 90 days from the date of this review. DMEPA found the proposed name, Prolia, acceptable in OSE Review #2008-1362 dated April 7, 2009. Additionally, on September 4, 2008, DDMAC reviewed the proposed name and had no concerns regarding the proposed name from a promotional perspective and did not offer any additional comments relating to the proposed name. Furthermore, the review Division did not have any concerns with the proposed name, Prolia, during our initial review.

2 METHODS

For the proposed proprietary name, DMEPA staff search a standard set of databases and information sources (see section 5) to identify names with orthographic and phonetic similarity to the proposed name that have been approved since the previous OSE proprietary name review. We used the same search criteria used in OSE Review #2008-1362 for the proposed proprietary name, Prolia. Since none of the proposed product characteristics were altered we did not re-evaluate previous names of concern. Additionally, DMEPA searches the USAN stem list to determine if the name contains any USAN stems as of the last USAN updates. DMEPA bases the overall risk assessment on the findings of a Failure Mode and Effects Analysis (FMEA) of the proposed proprietary name, and focuses on the avoidance of medication errors.

3 RESULTS

3.1 DATABASES

The searches of the databases referenced in Section 5 yielded 11 new names as having some similarity to the name Prolia.

Nine of the 11 names were thought to look like Prolia, which include: Drolex, Duotan, Pralax, Proair HFA, Prolac, Prolax, (b) (4), Protec, and Ralix. One additional name, Pylera, was thought to sound similar to Prolia. One name, Prolibra, was thought to look and sound similar to Prolia.

Additionally, DMEPA staff did not identify any United States Adopted Names (USAN) stems in the proposed proprietary name, as of March 8, 2010.

3.2 SAFETY EVALUATOR RISK ASSESSMENT

Independent searches by the primary Safety Evaluator identified no additional names which were thought to look or sound similar to Prolia and represent a potential source of drug name confusion.

Upon further observation, five of the 11 names (Drolex, Pralax, Prolac, Prolax, and (b) (4) were found to be foreign drug names. Additionally, two of the 11 names (Duotan and Pylera) lacked orthographic and/or phonetic similarity. Therefore, these seven names were not evaluated further.

We evaluated the remaining four names for their similarity to the proposed name. The FMEA indicates that the proposed name, Prolia, is not likely to result in name confusion that could lead to medication errors with any of the four names for the reasons listed in Appendix A and B.

4 CONCLUSIONS AND RECOMMENDATIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Prolia, is not vulnerable to name confusion that could lead to medication errors. Thus, the Division of Medication Error Prevention and Analysis (DMEPA) has no objection to the proprietary name, Prolia, for this product at this time.

DMEPA considers this a final review; however, if approval of the BLA is delayed beyond 90 days from the date of this review, the Division of Reproductive and Urologic Products or the Division of Biologic Oncology Products should notify DMEPA because the proprietary name must be re-reviewed prior to the new approval date.

5 REFERENCES

1. Micromedex Integrated Index (http://weblern/)

Contains a variety of databases covering pharmacology, therapeutics, toxicology and diagnostics.

2. Phonetic and Orthographic Computer Analysis (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion. This is a database which was created for the Medication Error Prevention Staff, FDA.

3. Drug Facts and Comparisons, online version, St. Louis, MO (http://weblern/)

Drug Facts and Comparisons is a compendium organized by therapeutic Course; contains monographs on prescription and OTC drugs, with charts comparing similar products.

4. AMF Decision Support System [DSS]

DSS is a government database used to track individual submissions and assignments in review divisions.

5. Division of Medication Error Prevention proprietary name consultation requests

This is a list of proposed and pending names that is generated by the Medication Error Prevention Staff from the Access database/tracking system.

6. Drugs@FDA (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm)

Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved brand name and generic drugs and therapeutic biological products; prescription and over-the-counter human drugs and therapeutic biologicals, discontinued drugs and "Chemical Type 6" approvals.

7. Electronic online version of the FDA Orange Book (http://www.fda.gov/cder/ob/default.htm)

Provides a compilation of approved drug products with therapeutic equivalence evaluations.

8. US Patent and Trademark Office location http://www.uspto.gov.

Provides information regarding patent and trademarks.

9. Clinical Pharmacology Online (http://weblern/)

Contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common, combination, nutraceutical and nutritional products. Provides a keyword search engine.

10. Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

The Pharma In-Use Search database contains over 400,000 unique pharmaceutical trademarks and tradenames that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

11. Natural Medicines Comprehensive Databases (http://weblern/)

Contains up-to-date clinical data on the natural medicines, herbal medicines, and dietary supplements used in the western world.

12. Stat!Ref (http://weblern/)

Contains full-text information from approximately 30 texts. Includes tables and references. Among the database titles are: Handbook of Adverse Drug Interactions, Rudolphs Pediatrics, Basic Clinical Pharmacology and Dictionary of Medical Acronyms Abbreviations.

13. USAN Stems (http://www.ama-assn.org/ama/pub/category/4782.html)

List contains all the recognized USAN stems.

14. Red Book Pharmacy's Fundamental Reference

Contains prices and product information for prescription, over-the-counter drugs, medical devices, and accessories.

15. Lexi-Comp (www.pharmacist.com)

A web-based searchable version of the Drug Information Handbook.

16. Medical Abbreviations Book

Contains commonly used medical abbreviations and their definitions.

17. Prior OSE Review

OSE Review # 2008-1362 – DMEPA Proprietary Name Review of Prolia. Park, Judy; April 7, 2009

APPENDICES

Appendix A: Products with no overlap in strength or dose

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose (if applicable)
Prolia (denosumab)		**60 mg/mL**	**Usual dose: Inject 60 mg (1 mL) subcutaenously once every 6 months**
ProTec	Look	Vitamins for smokers; Complex of 18 Natural Amino Acids (strength not available)	2 capsules per day
Prolibra	Look and Sound	All-natural, whey derived ingredient for weight loss products. (strength not available)	Not applicable.

Appendix B: Single strength product with different product characteristics

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose (if applicable)	Differentiating Product Characteristics
Prolia (denosumab)		**60 mg/mL**	**Usual dose: Inject 60 mg (1 mL) subcutaenously once every 6 months**	
Proair HFA (Albuterol Sulfate)	Look	108 mcg/ actuation	2 inhalations every 4-6 hours as needed	Dosage form (inhalation solution vs. injectable), route of administration (inhalation vs. subcutaneous), frequency of administration (every 4-6 hours vs. once every 6 months), dose (2 inhalations vs. 60 mg)
Ralix (Chlorpheniramine/ Methscopolamine/ Phenylephrine)	Look	Extended-release Tablet: 8 mg/ 2.5 mg/ 40 mg	1 tablet every 12 hours	Dosage form (tablet vs. injectable), route of administration (oral vs. subcutaneous), frequency of administration (every 12 hours vs. once every 6 months), dose (1 tablet vs. 60 mg)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring Maryland 20993

PROPRIETARY NAME REQUEST
- CONDITIONALLY ACCEPTABLE

MAY 20 2009

STN: BL 125320/0
STN: BL 125331/0
STN: BL 125332/0
STN: BL 125333/0

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

Dear Dr. Burd:

Please refer to your Biologics License Application (BLA) dated December 19, 2008, received December 19, 2008, submitted under section 351 of the Public Health Service Act, for Prolia (denosumab).

We also refer to your January 15, 2009, correspondence, received January 16, 2009, requesting review of your proposed proprietary name, Prolia. We have completed our review of the proposed proprietary name, Prolia, and have concluded that it is acceptable.

The proposed proprietary name, Prolia, will be re-reviewed 90 days prior to the approval of the BLA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your January 15, 2009, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Darrell Jenkins, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0558. For any other information regarding this application, contact Celia Peacock, MPH, RD, Regulatory Project Manager, in the Division of Reproductive and Urologic Products, Office of New Drugs (OND).

Sincerely,

{See appended electronic signature page}

George Benson

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

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 7, 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, Acting Team Leader Cmena 4/7/09
Denise Toyer, PharmD, Deputy Director D.P. Toyer 4/7/09.
Carol Holquist, RPh, Director D.P. Toyer for Carol Holquist 4/7/09
Division of Medication Errors and Technical Support

From: Judy Park, PharmD, Safety Evaluator Judy Park 4/7/09
Division of Medication Errors and Technical Support

Subject: Proprietary Name Review

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

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

Applicant: Amgen

OSE RCM #: 2008-1362

****Note: This review contains proprietary and confidential information that should not be released to the public.****

CONTENTS

EXECUTIVE SUMMARY

DMEPA identified 29 names as having potential orthographic and/or phonetic similarity to Prolia. Additionally, the Applicant submitted an external risk assessment of the proprietary name, which identified an additional two names. Thus, DMEPA analyzed 31 names for their potential to cause confusion with Prolia. Our Failure Mode Effects Analysis determined that the name similarity between Prolia and the 31 names was unlikely to result in medication errors related to name confusion. This finding was consistent with and supported by the external risk assessment of the proprietary name submitted by the Applicant. Thus the Division of Medication Error Prevention and Analysis (DMEPA) has no objection to the proprietary name, Prolia, for this product. The Division of Reproductive and Urologic Products and the Division of Biologic Oncology Products concur with this assessment.

However, if any of the proposed product characteristics as stated in this review are altered prior to approval of the product, DMEPA rescinds this Risk Assessment finding and the name must be resubmitted for review. In the event that our Risk Assessment finding is rescinded, the evaluation of the name on resubmission is independent of the previous Risk Assessment, and as such, the conclusions on re-review of the name are subject to change.

In addition, the proposed name must be reevaluated 90 days before approval of the NDA, even if the proposed product characteristics as stated in this review are not altered.

1 BACKGROUND

1.1 INTRODUCTION

This review is in response to a request from the Division of Reproductive and Urologic Products and the Division of Biologic Oncology Products for assessment of the proposed proprietary name, Prolia, regarding its potential confusion with other proprietary or established drug names in normal practice settings.

Additionally, container labels, carton and insert labeling were provided for review and comment and will be reviewed in a separate review (OSE Review #2009-162).

1.2 PRODUCT INFORMATION

Prolia (denosumab) is a receptor activator of nuclear factor kappa B (RANK) ligand inhibitor indicated for treatment and prevention of postmenopausal osteoporosis and treatment and prevention of bone loss associated with hormone ablation therapy with prostate and breast cancer. The recommended dose is 60 mg (1 mL) once every 6 months via subcutaneous injection. It is available in 60 mg/mL solution in a single-use prefilled syringe and single-dose vial.

2 METHODS AND MATERIALS

This section consists of two sections which describe the methods and materials used by DMEPA conducting a proprietary name risk assessment (see 2.1 Proprietary Name Risk Assessment) and label, labeling, and/or packaging risk assessment (see 2.2 Label and Labeling Risk Assessment). The primary focus for both of the assessments is to identify and remedy potential sources of medication error prior to drug approval. The Division of Medication Error Prevention defines a

medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [1]

2.1 PROPRIETARY NAME RISK ASSESSMENT

FDA's Proprietary Name Risk Assessment considers the potential for confusion between the proposed proprietary name, Prolia, and the proprietary and established names of drug products existing in the marketplace and those pending IND, NDA, BLA, and ANDA products currently under review by the Agency.

For the proprietary name, Prolia, DMEPA searches a standard set of databases and information sources to identify names with orthographic and phonetic similarity (see Sections 2.1.1 for detail) and held an CDER Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name (see 2.1.1.2). Our Division also conducts internal CDER prescription analysis studies (see 2.1.2), and, when provided, external prescription analysis studies results are considered and incorporated into the overall risk assessment (see detail 2.1.4).

The Safety Evaluator assigned to the Proprietary Name Risk Assessment is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name (see detail 2.1.4). The overall risk assessment is based on the findings of a Failure Mode and Effects Analysis (FMEA) of the proprietary name, and is focused on the avoidance of medication errors. FMEA is a systematic tool for evaluating a process and identifying where and how it might fail. [2] FMEA is used to analyze whether the drug names identified with look- or sound-alike similarity to the proposed name could cause confusion that subsequently leads to medication errors in the clinical setting. DMEPA uses our clinical expertise to anticipate the conditions of the clinical setting that the product is likely to be used in based on the characteristics of the proposed product.

In addition, the product characteristics provide the context for the verbal and written communication of the drug names and can interact with the orthographic and phonetic attributes of the names to increase the risk of confusion when there is overlap, or, in some instances, decrease the risk of confusion by helping to differentiate the products through dissimilarity. As such, the staff consider the product characteristics associated with the proposed drug throughout the risk assessment, since the product characteristics of the proposed may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed drug name include, but are not limited to established name of the proposed product, the proposed indication, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. Because drug name confusion can occur at any point in the medication use process,

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[1] National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/aboutMedErrors.html. Last accessed 10/11/2007.

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

DMEPA considers the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.[3]

2.1.1 Search Criteria

DMEPA considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted as outlined in Appendix A.

For this review, particular consideration was given to drug names beginning with the letter 'P' when searching to identify potentially similar drug names, as 75% of the confused drug names reported by the USP-ISMP Medication Error Reporting Program involve pairs beginning with the same letter.[4][5]

To identify drug names that may look similar to Prolia, the staff also consider the orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (six letters), upstrokes (two, capital letter 'P' and lower case 'l'), downstokes (none), cross-strokes (none), and dotted letters (one, lower case 'i'). Additionally, several letters in Prolia may be vulnerable to ambiguity when scripted, including the letter 'P' may appear as 'B,' 'D,' 'F,' or 'R'; lower case 'r' may appear as a lower case 'i' ; lower case 'a,' 'i,' or 'o' may appear as 'a,' 'e,' 'i,' 'o,' or 'u'. As such, the staff also considers these alternate appearances when identifying drug names that may look similar to Prolia.

When searching to identify potential names that may sound similar to Prolia, DMEPA searches for names with similar number of syllables (two), stresses (pro-LIA or PRO-lia), and placement of vowel and consonant sounds. Additionally, several letters in Prolia may be vulnerable to misinterpretation when spoken, including 'Pro' may be interpreted as 'Fro,' 'Tro,' or 'Bro.' As such, the staff also considers these alternate pronunciations when identifying drug names that may sound similar to Prolia. The Applicant's intended pronunciation of the proprietary name could not be expressly taken into consideration, as this was not provided with the proposed name submission.

The staff also consider the product characteristics associated with the proposed drug throughout the identification of similar drug names, since the product characteristics of the proposed drug ultimately determine the use of the product in the clinical practice setting For this review, DMEPA was provided with the following information about the proposed product: the proposed proprietary name (Prolia), the established name (denosumab), proposed indication (postmenopausal osteoporosis and bone loss in patients undergoing hormone ablation for prostate and breast cancer), strength (60 mg/mL), dose (60 mg), frequency of administration (once every 6 months), route (subcutaneous) and dosage form (injectable) of the product. Appendix A provides a more detailed listing of the product characteristics the staff generally takes into consideration.

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[3] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

[4] Institute for Safe Medication Practices. Confused Drug name List (1996-2006). Available at http://www.ismp.org/Tools/confuseddrugnames.pdf

[5] Kondrack, G and Dorr, B. Automatic Identification of Confusable Drug Names. Artifical Inteligence in Medicine (2005)

Lastly, DMEPA also consider the potential for the proposed name to inadvertently function as a source of error for reasons other than name confusion. Post-marketing experience has demonstrated that proprietary names (or components of the proprietary name) can be a source of error in a variety of ways. As such, these broader safety implications of the name are considered and evaluated throughout this assessment and DMEPA provide additional comments related to the safety of the proposed name or product based on their professional experience with medication errors.

2.1.1.1 Database and information sources

The proposed proprietary name, Prolia, was provided to DMEPA to conduct a search of the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to Prolia using the criteria outlined in 2.1.1. A standard description of the databases used in the searches is provided in Section 7. To complement the process, DMEPA use a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, DMEPA review the USAN stem list to determine if any USAN stems are present within the proprietary name. The findings of the individual Safety Evaluators were then pooled and presented to the Expert Panel.

2.1.1.2 CDER Expert Panel Discussion

An Expert Panel Discussion is held by DMEPA to gather CDER professional opinions on the safety of the product and the proprietary name, Prolia. Potential concerns regarding drug marketing and promotion related to the proposed names are also discussed. This group is composed of DMEPA and representatives from the Division of Drug Marketing, Advertising, and Communications (DDMAC).

The pooled results of DMEPA were presented to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend the addition of names, additional searches by the Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name.

2.1.2 FDA Prescription Analysis Studies

Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Prolia with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The studies employ a total of 123 healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The results are used by the Safety Evaluator to identify any orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

In order to evaluate the potential for misinterpretation of Prolia in handwriting and verbal communication of the name, inpatient medication orders and outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These prescriptions are optically scanned and one prescription is delivered to a random sample of 123 participating health professionals via e-mail. In addition, a verbal

prescription is recorded on voice mail. The voice mail messages are then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants send their interpretations of the orders via e-mail to DMEPA.

Figure 1. Prolia Study (conducted on October 10, 2008)

HANDWRITTEN PRESCRIPITON AND MEDICATION ORDER	VERBAL INPATIENT ORDER
Outpatient Prescription: Prolia #1 syringe Return to clinic 6mos for injection	Prolia Quantity 1 syringe Return to clinic every 6 months for injection
Inpatient Medication Order: Prolia inject subcutaneously x 1 dose	

2.1.3 External Proprietary Name Risk Assessment

For this product, the Applicant submitted an independent risk assessment of the proposed proprietary name conducted by a consulting firm. DMEPA conducts an independent analysis and evaluation of the data provided, and responds to the overall findings of the assessment. When the external proprietary name risk assessment identifies potentially confusing names that were not captured in DMEPA's database searches or in the Expert Panel Discussion, these names are included in the Safety Evaluator's Risk Assessment and analyzed independently by the Safety Evaluator to determine if the potentially confusing name could lead to medication errors in usual practice settings.

After the Safety Evaluator has determined the overall risk assessment of the proposed name, the Safety Evaluator compares the findings of their overall risk assessment with the findings of the proprietary name risk assessment submitted by the Applicant. The Safety Evaluator then determines whether DMEPA's risk assessment concurs or differs with the findings. When the proprietary name risk assessments differ, DMEPA provides a detailed explanation of these differences.

2.1.4 Comments from the OND Review Division

DMEPA requests the regulatory division in the Office of New Drugs responsible for the application for their comments or concerns with the proposed proprietary name and any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with DDMAC's decision on the name. Any comments or concerns are addressed in the safety evaluator's assessment.

The regulatory division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name. The regulatory division is requested to concur/not concur with DMEPA's final decision.

2.1.5 Safety Evaluator Risk Assessment of the Proposed Proprietary Name

Based on the criteria set forth in Section 2.1.1, the Safety Evaluator Risk Assessment applies their individual expertise gained from evaluating medication errors reported to FDA to conduct a Failure Mode and Effects Analysis and provide an overall risk of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.[6] When applying FMEA to assess the risk of a proposed proprietary name, DMEPA seeks to evaluate the potential for a proposed name to be confused with another drug name as a result of the name confusion and cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to look- or sound-alike drug names prior to approval, where actions to overcome these issues are easier and more effective then remedies available in the post-approval phase.

In order to perform an FMEA of the proposed name, the Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product is not yet marketed, the Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product characteristics listed in Appendix A. The Safety Evaluator then analyzes the proposed proprietary name in the context of the usual practice setting and works to identify potential failure modes and the effects associated with the failure modes.

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, expert panel evaluation, and studies, and identifies potential failure modes by asking: "Is the name Prolia convincingly similar to another drug name, which may cause practitioners to become confused at any point in the usual practice setting?" An affirmative answer indicates a failure mode and represents a potential for Prolia to be confused with another proprietary or established drug name because of look- or sound-alike similarity. If the answer to the question is no, the Safety Evaluator is not convinced that the names posses similarity that would cause confusion at any point in the medication use system and the name is eliminated from further review.

In the second stage of the Risk Assessment, all potential failure modes are evaluated to determine the likely *effect* of the drug name confusion, by asking "Could the confusion of the drug names conceivably result in medication errors in the usual practice setting?" The answer to this question is a central component of the Safety Evaluator's overall risk assessment of the proprietary name. If the Safety Evaluator determines through FMEA that the name similarity would ultimately not be a source of medication errors in the usual practice setting, the name is eliminated from further analysis. However, if the Safety Evaluator determines through FMEA that the name similarity could ultimately cause medication errors in the usual practice setting, the Safety Evaluator will then recommend that an alternate proprietary name be used. In rare instances, the FMEA findings may provide other risk-reduction strategies, such as product

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

reformulation to avoid an overlap in strength or an alternate modifier designation may be recommended as a means of reducing the risk of medication errors resulting from drug name confusion.

DMEPA will object to the use of proposed proprietary name when the one or more of the following conditions are identified in the Safety Evaluator's Risk Assessment:

1. DDMAC finds the proposed proprietary name misleading from a promotional perspective, and the review Division concurs with DDMAC's findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a trade name or otherwise. [21 U.S.C 321(n); see also 21 U.S.C. 352(a) & (n)].
2. DMEPA identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].
3. FMEA identifies potential for confusion between the proposed proprietary name and other proprietary or established drug names, and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.
4. The proposed proprietary name contains an USAN stem, particularly in a manner that is contradictory to the USAN Council's definition.
5. DMEPA identifies a potential source of medication error within the proposed proprietary name. The proprietary name may be misleading, or inadvertently introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug another drug product.

In the event that DMEPA objects to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, we will provide a contingency objection based on the date of approval: whichever product is awarded approval first has the right to the use the name, while we will recommend that the second product to reach approval seek an alternative name.

If none of these conditions are met, then DMEPA will not object to the use of the proprietary name. If any of these conditions are met, then our division will object to the use of the proprietary name. The threshold set for objection to the proposed proprietary name may seem low to the Applicant; however, the safety concerns set forth in criteria 1 through 5 are supported either by FDA Regulation or by external healthcare authorities, including the Institute of Medicine, the World Health Organization, the Joint Commission, and the Institute for Safe Medication Practices, that have examined medication errors resulting from look- or sound-alike drug names and called for Regulatory Authorities to address the issue prior to approval.

Furthermore, DMEPA contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and preventable source of medication error that, in many instances, can be identified and remedied prior to approval to avoid patient harm.

Additionally, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to remedy post-approval. Educational efforts and so on are low-leverage strategies that have proven to have limited effectiveness at alleviating the medication errors involving drug name confusion. Higher-leverage strategies, such as drug name changes, have been undertaken in the past; but at great financial cost to the Applicant, and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for the approving the error-prone proprietary name. Moreover, even after Applicant's have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioner's vocabulary, and as such, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, DMEPA believes that post-approval efforts at reducing name confusion errors should be reserved for those cases in which the potential for name confusion could not be predicted prior to approval (see limitations of the process).

If DMEPA objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the FMEA process is used to identify strategies to reduce the risk of medication errors. Our Division is likely to recommend that the Applicant select an alternative proprietary name and submit the alternate name to the Agency for DMEPA to review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name, and so we may be able to provide the Applicant with recommendations that reduce or eliminate the potential for error would render the proposed name acceptable.

3 RESULTS

3.1 PROPRIETARY NAME RISK ASSESSMENT

3.1.1 Database and Information Sources

The database, internet, and reference search identified 27 names as having some similarity to the name Prolia.

Twenty of the 27 names were thought to look like Prolia, which include: Droxia, Prozac, (b) (4) (b) (4), (b) (4), Prolex DM, Prelone, Prelief, Proline, Prelu-2, Prolixin, Proloid, (b) (4) (b) (4) Prohist, Protid, (b) (4)***, Priftin, and (b) (4)***. Two names (b) (4) and Propecia) were thought to sound similar to Prolia. Five additional names (Prolief, Portia, Prolic, (b) (4), and Prolia) were thought to look and sound similar to Prolia.

A search of the United States Adopted Names (USAN) stem list on February 10, 2009 indentified no USAN stems contained in the proposed name, Prolia.

3.1.2 Expert Panel Discussion

The Expert Panel reviewed the pool of names identified by DMEPA staff (see section 3.1.1. above), and noted no additional names thought to have orthographic or phonetic similarity to Prolia

*** **Note: This review contains proprietary and confidential information that should not be released to the public.** ***

DDMAC had no concerns regarding the proposed name from a promotional perspective, and did not offer any additional comments relating to the proposed name.

3.1.3 FDA Prescription Analysis Studies

A total of 29 practitioners responded, but none of the responses overlapped with any existing or proposed drug names. All the respondents in the written studies (n=17) and five respondents from the verbal study interpreted the name correctly as "Prolia." All the misinterpretations occurred in the phonetic prescription study with the vowels in Prolia 'i' reported as 'e' as well as the consonants 'Pr' reported as 'Per' and 'l' reported as 'v'. See Appendix B for the complete listing of interpretations from the verbal and written prescription studies.

3.1.4 External Name Studies

In the proposed name risk assessment submitted by the Applicant, Drug Safety Institute (DSI) identified and evaluated a total of 180 drug names thought to have some potential for confusion with the name Prolia.

One hundred sixty-five (n=165) of the 180 names were determined to lack sufficient orthographic and/or phonetic similarity to Prolia to present a risk of confusion. Thirteen (n=13) of the 180 names (Droxia, Prozac, Prolex DM, Prelone, Prelief, Proline, Prelu-2, Prolixin, Proloid, Protid (b) (4), Propecia, and Portia) were previously identified in the DMEPA staff searches or the Expert Panel Discussion. The remaining two names, Plova and Solia, were determined to have orthographic and /or phonetic similarity to Prolia, and thus determined to present some risk of confusion.

3.1.5 Comments from the OND Review Division

DMEPA notified the Division of Reproductive and Urologic Products (DRUP) and the Division of Biology Oncology Products (DBOP) via e-mail that we had no objections to the proposed proprietary name, Prolia, on March 5, 2009. Per e-mail correspondences from DRUP on March 9, 2009 and DBOP on March 31, 2009, they indicated they concur with our assessment of the proposed proprietary name, Prolia.

3.1.6 Safety Evaluator Risk Assessment

Independent searches by the primary Safety Evaluator identified two additional names, Frova and Pruvel***, thought to look similar to Prolia and represent a potential source of drug name confusion.

Eight of the 31 identified names were determined to lack sufficient orthographic and/or phonetic similarity to Prolia to present a risk of confusion (see Appendix C). The remaining 23 names were determined to have some orthographic and /or phonetic similarity to Prolia, and thus determined to present some risk of confusion.

Failure mode and effect analysis (FMEA) was then applied to determine if the potential name, Prolia, could potentially be confused with any of these 23 names and lead to medication errors.

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This analysis determined that the name similarity between Prolia and the identified names was unlikely to result in medication errors for all 23 products for the reasons described in Appendices D through H.

4 DISCUSSION

Thirty-one names were evaluated for their potential similarity to the proposed name, Prolia. The FMEA indicates that the proposed name is not likely to result in name confusion that could lead to medication error for the reasons outlined in Appendices C through H.

5 CONCLUSIONS AND RECOMMENDATIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Prolia, is not vulnerable to name confusion that could lead to medication errors. This finding was consistent with and supported by an independent risk assessment of the proprietary name submitted by the Applicant. As such, the Division of Medication Error Prevention and Analysis (DMEPA) has no objection to the proprietary name, Prolia, for this product at this time. The Division of Reproductive and Urologic Products and the Division of Biologic Oncology Products concur with this assessment. Additionally, DDMAC does not object to the proposed name, Prolia, from a promotional perspective.

However, if any of the proposed product characteristics as stated in this review are altered prior to approval of the product, DMEPA rescinds this Risk Assessment finding and the name must be resubmitted for review. In the event that our Risk Assessment finding is rescinded, the evaluation of the name on resubmission is independent of the previous Risk Assessment, and as such, the conclusions on re-review of the name are subject to change. If the approval of this application is delayed beyond 90 days from the signature date of this review, the proposed name must be resubmitted for evaluation.

5.1 COMMENTS TO THE DIVISION

We would appreciate feedback of the final outcome of this review. We would be willing to meet with the Divisions for further discussion, if needed. 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, please contact OSE Project Managers, Sandra Griffith at 301-796-2445 or Cherye Milburna at 301-796-2084.

5.2 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Prolia, and have concluded that it is acceptable.

The proprietary name, Prolia, will be re-reviewed 90 days prior to approval of the BLA. If we find the name unacceptable following the re-review, we will notify you.

If any of the proposed product characteristics are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

6 REFERENCES

1. ***Micromedex Integrated Index***
(http://inside.fda.gov/Library/ElectronicResourcesWebLERN/Alphabeticallist/index.htm)

Contains a variety of databases covering pharmacology, therapeutics, toxicology and diagnostics.

2. ***Phonetic and Orthographic Computer Analysis (POCA)***

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion. This is a database which was created for DMEPA, FDA.

3. ***Drug Facts and Comparisons, online version, St. Louis, MO***
(http://inside.fda.gov/Library/ElectronicResourcesWebLERN/Alphabeticallist/index.htm)

Drug Facts and Comparisons is a compendium organized by therapeutic Course; contains monographs on prescription and OTC drugs, with charts comparing similar products.

4. ***AMF Decision Support System [DSS]***

DSS is a government database used to track individual submissions and assignments in review divisions.

5. ***Division of Medication Error Prevention proprietary name consultation requests***

This is a list of proposed and pending names that is generated by DMEPA from the Access database/tracking system.

6. ***Drugs@FDA*** *(http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm)*

Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved brand name and generic drugs and therapeutic biological products; prescription and over-the-counter human drugs and therapeutic biologicals, discontinued drugs and "Chemical Type 6" approvals.

7. ***Electronic online version of the FDA Orange Book***
(http://www.fda.gov/cder/ob/default.htm)

Provides a compilation of approved drug products with therapeutic equivalence evaluations.

8. ***US Patent and Trademark Office location*** *http://www.uspto.gov.*

Provides information regarding patent and trademarks.

9. ***Clinical Pharmacology Online*** *(http://inside.fda.gov/Library/ElectronicResourcesWebLERN/Alphabeticallist/index.htm)*

Contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common, combination, nutraceutical and nutritional products. Provides a keyword search engine.

10. ***Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at*** *www.thomson-thomson.com*

The Pharma In-Use Search database contains over 400,000 unique pharmaceutical trademarks and tradenames that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

11. ***Natural Medicines Comprehensive Databases*** *(http://inside.fda.gov/Library/ElectronicResourcesWebLERN/Alphabeticallist/index.htm)*

Contains up-to-date clinical data on the natural medicines, herbal medicines, and dietary supplements used in the western world.

12. ***Stat!Ref*** *(http://inside.fda.gov/Library/ElectronicResourcesWebLERN/Alphabeticallist/index.htm)*

Contains full-text information from approximately 30 texts. Includes tables and references. Among the database titles are: Handbook of Adverse Drug Interactions, Rudolphs Pediatrics, Basic Clinical Pharmacology and Dictionary of Medical Acronyms Abbreviations.

13. ***USAN Stems (http://www.ama-assn.org/ama/pub/category/4782.html)***

List contains all the recognized USAN stems.

14. ***Red Book Pharmacy's Fundamental Reference***

Contains prices and product information for prescription, over-the-counter drugs, medical devices, and accessories.

15. ***Lexi-Comp (www.pharmacist.com)***

A web-based searchable version of the Drug Information Handbook.

16. ***Medical Abbreviations Book***

Contains commonly used medical abbreviations and their definitions.

APPENDICES

Appendix A:

DMEPA considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. DMEPA also compare the spelling of the proposed proprietary name with the proprietary and established name of existing and proposed drug products because similarly spelled names may have greater likelihood to sound similar to one another when spoken or look similar to one another when scripted. DMEPA also examine the orthographic appearance of the proposed name using a number of different handwriting samples. Handwritten communication of drug names has a long-standing association with drug name confusion. Handwriting can cause similarly *and* dissimilarly spelled drug name pairs to appear very similar to one another and the similar appearance of drug names when scripted has lead to medication errors. DMEPA apply their expertise gained from root-cause analysis of such medication errors to identify sources of ambiguity within the name that could be introduced when scripting (i.e. "T" may look like "F," lower case 'a' looks like a lower case 'u,' etc), along with other orthographic attributes that determine the overall appearance of the drug name when scripted (see detail in Table 1 below). Additionally, since verbal communication of medication names is common in clinical settings, DMEPA compare the pronunciation of the proposed proprietary name with the pronunciation of other drug names. If provided, DMEPA will consider the Applicant's intended pronunciation of the proprietary name. However, because the Applicant has little control over how the name will be spoken in practice, DMEPA also considers a variety of pronunciations that could occur in the English language.

Table 1. Criteria used to identify drug names that look- or sound-similar to a proposed proprietary name

Type of similarity	Considerations when searching the databases		
	Potential causes of drug name similarity	Attributes examined to identify similar drug names	Potential Effects
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	• Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communication • Names may look similar when scripted and lead to drug name confusion in written communication
	Orthographic similarity	Similar spelling Length of the name Upstrokes Downstrokes Cross-strokes Dotted letters Ambiguity introduced	• Names may look similar when scripted, and lead to drug name confusion in written communication

		by scripting letters Overlapping product characteristics	
Sound-alike	Phonetic similarity	Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics	• Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Appendix B:

CDER Prescription Study Responses

Prolia	Prolia	Prolia
Prolia	Prolia	Prolia
Prolia	Prolia	Prolea
Prolia	Prolia	Prolia
Prolia	Prolia	Provia
Prolia	Prolia	Prolea
Prolia	Prolia	Prolea
Prolia	Prolia	Prolia
Prolia		Perlia
		Prolia
		Prolea
		Provia

Appendix C: Proprietary names with minimal orthographic and/or phonetic similarity

Proprietary Name	Similarity to Prelu
Prelief	Look
Prelu-2	Look
Priftin	Look
Prohist	Look
Prolief	Look
Prolixin	Look
(b) (4)	Sound
Propecia	Sound

Appendix D: Proprietary names used only in Foreign Countries

Proprietary Name	Similarity to Prelu	Country
Prolic	Look and Sound	Indonesia
Prolidon	Look	Mexico
(b) (4)	Look	Chile, Argentina, Brazil, Venezuela
(b) (4)	Look and Sound	Peru, Philippines

Appendix E: Proprietary name of products discontinued with no generic equivalent

Proprietary Name	Similarity to Prelu	Year discontinued
Plova (psyllium mucilloid) (Over-the-Counter)	Look	Not available
Proloid (thyroglobulin)	Look	Not available

Appendix F: Non-Drug Names

Proprietary Name	Similarity to Prolia	Reason
(b) (4)	Look	Chemical
Prolia	Look and Sound	Soy flour
(b) (4)	Look	Chemical

Appendix G: Proprietary names of products withdrawn or approved under a different tradename

Proprietary Name	Similarity to Prolia	Reason (year, if applicable)
(b) (4)***	Look	(b) (4)
(b) (4)***	Look	
(b) (4)***	Look	

Appendix H: Products with no overlap in strength, usual dose and route of administration

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose (if applicable)
Prolia (denosumab)		**60 mg/mL**	**Usual dose: Inject 60 mg (1 mL) subcutaenously once every 6 months**
Droxia (Hydroxyurea)	Look	200 mg, 300 mg, 400 mg	15 mg/kg/day orally
Frova (Frovatriptan Succinate)	Look	2.5 mg	1 tablet once orally
Portia (Ethinyl Estradiol/ Levonorgestrel)	Look and Sound	0.03 mg/0.15 mg	1 tablet daily orally
Prelone (Prednisolone)	Look	15 mg/mL	Individualized to patient; orally

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Prodec DM (Carbinoxamine/ Dextromethorphan/ Pseudoephedrine)	Look	2 mg/4 mg/25 mg	1 dropperful orally every 6 hours
Prolex DM (Guiafenesin/ Dextromethorphan)	Look	300 mg/15 mg per 5 mL	5 to 7.5 mL orally up to four times daily
Proline (amino acid)	Look	500 mg	3000 mg per day taken twice daily orally
Protid (Acetaminophen/ Chlorpheniramine/ Phenylephrine)	Look	500 mg/8 mg/40 mg	1-3 tablets once to three times daily orally
Prozac (Fluoxetine)	Look	Capsule: 10 mg, 20 mg, 40 mg, 90 mg Solution: 20 mg/5 mL	Individualized to patient; usually start at 20 mg/day orally
Pruvel*** (Prulifoxacin)	Look	600 mg	1 tablet orally daily for 3 days
Solia (Ethinyl Estradiol/ Desogestrel)	Look	0.03 mg/0.15 mg	1 tablet daily orally

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

BLA 125320

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Amgen Inc.
One Amgen Center Drive
Mail Stop 17-2-B
Thousand Oaks, CA 91320-1799

ATTENTION: Edward S. Burd, PhD
Senior Manager, Regulatory Affairs

Dear Dr. Burd:

Please refer to your Biologics License Application (BLA) dated December 19, 2008, received December 19, 2008, submitted under section 351 of the Public Health Service Act, for Denosumab Injection, 60 mg/mL.

We also refer to your February 26, 2010, correspondence, received February 26, 2010, requesting review of your proposed proprietary name, Prolia. We have completed our review of the proposed proprietary name, Prolia and have concluded that it is acceptable.

The proposed proprietary name, Prolia, will be re-reviewed 90 days prior to the approval of the BLA. If we find the name unacceptable following the re-review, we will notify you. If **any** of the proposed product characteristics as stated in your February 26, 2010 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Maria Wasilik, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0567.

For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Nenita Crisostomo at (301) 796-0875.

Sincerely,
Denise P. Toyer, Deputy Director for
{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research