

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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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: October 18, 2010

Application Type/Number: NDA 022512

Through: Zachary Oleszczuk, PharmD, Team Leader
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Division of Medication Error Prevention and Analysis

From: Cathy A. Miller, MPH, BSN, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Proprietary Name Review and Labels and Labeling Review

Drug Name(s): Pradaxa (Dabigatran Etexilate) Capsules
75 mg and 150 mg

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.

OSE RCM #: 2010-1432

1 INTRODUCTION

This re-assessment of the proposed proprietary name, Pradaxa, is written in response to the anticipated approval of this NDA within 90 days from the date of this review. DMEPA found the proposed name, Pradaxa, acceptable in OSE Reviews #2006-938, dated September 21, 2007, and 2010-957, dated May 10, 2010. DDMAC reviewed the proposed name on December 13, 2006, November 25, 2009, and July 15, 2010, and had no concerns regarding the proposed name from a promotional perspective. Furthermore, the review Division did not have any concerns with the proposed name, Pradaxa, during our initial review.

2 REGULATOR HISTORY

DMEPA found the proprietary name, Pradaxa, acceptable in the IND phase (OSE Review #2006-938 dated September 21, 2007).

In OSE #2010-957 review of the proposed name, Pradaxa, NDA 022512 dated May 10, 2010, DMEPA again found the proposed name, Pradaxa, acceptable. In OSE #2010-957 final review of the proposed proprietary name, Pradaxa, DMEPA also found the name acceptable. However, prior to the final signoff of this review, the Division of Cardiovascular and Renal Products (DCRP) notified DMEPA in an email communication dated September 22, 2010, that they would only be approving the 150 mg strength for this product. This change in product characteristics created a potential for name confusion with the existing product, Prenexa, due to orthographic and phonetic similarities, along with other overlapping product characteristics including single strength availability, oral capsule dosage form and oral route of administration.

In a teleconference dated October 4, 2010 between representatives of the Division of Cardiovascular and Renal Products (DCRP), DMEPA and the Applicant, DMEPA informed the Applicant of the potential for confusion between the proposed name Pradaxa and the currently marketed drug Prenexa and our decision that because of the potential confusion between the two names, DMEPA finds the name unacceptable.

On October 5, 2010, the Applicant submitted a request for the review of proposed proprietary name, (b) (4), along with submission of proposed contain labels and carton labeling that incorporated the proposed name, (b) (4).

However, during the review team's labeling meeting on October 14, 2010, the review division informed DMEPA that they would be approving Pradaxa in both the 75 mg and 150 mg strengths. Thus, the Applicant withdrew the proposed proprietary name, (b) (4) and requested the reconsideration of the proposed name Pradaxa.

3 METHODS

For the proposed proprietary name, DMEPA staff search a standard set of databases and information sources (see Section 4) 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 Reviews #2006-938 and #2010-957 for the proposed proprietary name, Pradaxa.

Additionally, the previous reviews of the proposed name Pradaxa evaluated 110 mg and 150 mg strengths. However, the Division has decided to approve a 75 mg strength along with the 150 mg strength, thus DMEPA re-evaluated all the names of concerns in the previous reviews (OSE Reviews #2006-938 dated September 21, 2007 and #2010-957 dated May 10, 2010), considering the 75 mg and 150 mg strengths to determine if any of the previous names of concerns created a potential for confusion.

DMEPA also searched the United States Adopted Names (USAN) stem list to determine if the name contains any USAN stems as of the last USAN. DMEPA based 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.

DMEPA provided comments on container labels, carton labeling and package insert labeling submitted by the Applicant on October 4, 2010 in OSE Review #2009-2234 dated October 14, 2010. Based on our

recommendations, the Applicant submitted revised container labels and carton labeling on October 14, 2010 which we also re-reviewed.

4 RESULTS AND DISCUSSION

Since the Division decided to approve both the 75 mg and 150 mg strengths of Pradaxa, our concern with drug name confusion between the proposed name Pradaxa and the marketed drug, Prenexa, has been mitigated.

Additionally, DMEPA's review of names from previous reviews (OSE Reviews #2006-938 and #2010-957) found that the change from the 110 strength to the 75 mg strength did not introduce the potential for name confusion with any of the products previously evaluated.

DMEPA staff did not identify any USAN stems in the proposed proprietary name, Pradaxa, as of October 13, 2010.

The searches of the databases yielded three new names, Krystexxa, Procardia, and Ranexa, thought to sound similar to Pradaxa and represent a potential source of drug name confusion. As such, we reviewed a total of three new names in this review. Our failure mode and effect analysis (FMEA) determined that the name similarity between Pradaxa and the three names identified was unlikely to result in medication errors in the usual practice setting (see Appendix A).

DMEPA's reviewed the revised container labels and carton labeling for Pradaxa 75 mg and 150 mg strength and found that the Applicant has addressed recommendations provided in our OSE Review #2009-2234. (see Appendices B and C for images).

5 CONCLUSIONS AND RECOMMENDATIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Pradaxa, is not vulnerable to name confusion that could lead to medication errors nor is the name considered promotional. Thus, the Division of Medication Error Prevention and Analysis has no objection to the proprietary name, Pradaxa, for this product at this time.

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

Additionally, we find that the revised container labels and carton labeling for Pradaxa 75 mg and 150 mg strength have addressed our recommendations. Because the container labels and carton labeling submitted on October 14, 2010 were presented with the word 'Tradename' as a placeholder for the proprietary name, we ask that the Applicant resubmit labels and labeling that are presented with the approved proprietary name, Pradaxa.

REFERENCES

1. OSE Reviews

1. OSE Review #2006-938 Proprietary Name Review for Pradaxa, September 21, 2007, Arnwine, K.
2. OSE Review #2010-957 Proprietary Name Review for Pradaxa, May 10, 2010, Park, J.
3. OSE Review #2009-2234 Labels and Labeling Review, October 14, 2010, Miller, C.

2. 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, generic drugs, therapeutic biological products, prescription and over-the-counter human drugs and discontinued drugs and “Chemical Type 6” approvals.

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

USAN Stems List contains all the recognized USAN stems.

4. Division of Medication Error Prevention and Analysis Proprietary Name Consultation Request

Compiled list of proposed proprietary names submitted to the Division of Medication Error Prevention and Analysis for review. The list is generated on a weekly basis from the Access database/tracking system.

APPENDICES

Appendix A: Products with multiple differentiating product and/or orthographic characteristics minimize the risk for medication errors

| Product name with potential for confusion | Similarity to proposed proprietary name | Dosage Form/ Strength | Usual Dose | Differentiating Product Characteristics |
|---|---|---|---|---|
| Pradaxa (Dabigatran Etexilate) | | Capsules: 75 mg and 150 mg | 75 mg or 150 mg (one capsule) orally twice daily | N/A |
| Krystexxa (Pegloticase) | Sound | Injectable: 8 mg/mL | 8 mg via intravenous infusion every 2 weeks | <u>Dosage form:</u> injectable vs. capsule <u>Route:</u> intravenous infusion vs. oral <u>Dose:</u> 8 mg vs. 75 mg or 150 mg <u>Frequency:</u> every 2 weeks vs. twice daily |
| Procardia (Nifedipine) | Look | Capsule: 10 mg (available), 20 mg (discontinued but generics available) | 10 mg to 20 mg three times daily | <u>Dose:</u> 10 mg or 20 mg vs. 75 mg or 150 mg <u>Frequency:</u> three times daily vs. twice daily <u>Orthographic differences:</u> Middle letters 'car' in Procardia makes the name longer; different location of upstroke 'd'; cross-stroke of 'x' in Pradaxa |
| Ranexa (Ranolazine) | Look | Tablet: 500 mg, 1000 mg | 500 mg to 1000 mg twice daily | <u>Dose:</u> 500 mg or 1000 mg vs. 75 mg or 150 mg <u>Orthographic differences:</u> no stroke in Ranexa vs. an upstroke letter 'd' in Pradaxa |

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**Department of Health and Human Services
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Center for Drug Evaluation and Research
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Date: May 10, 2010

To: Norman Stockbridge, MD, Director
Division of Cardiovascular and Renal Products

Through: Carlos Mena-Grillasca, RPh, Team Leader
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From: Judy Park, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Proprietary Name Review

Drug Name(s): Pradaxa (Dabigatran Etexilate) Capsules
110 mg and 150 mg

Application Type/Number: NDA 022512

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.

OSE RCM #: 2010-957

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EXECUTIVE SUMMARY

Pradaxa is the proposed proprietary name for Dabigatran Etexilate Capsules. This proposed name was evaluated from a safety and promotional perspective based on the product characteristics provided by the Applicant. We sought input from pertinent disciplines involved with the review of this application and considered it accordingly. Our evaluation did not identify concerns that would render the name unacceptable based on the product characteristics and safety profile known at the time of this review. Thus, DMEPA finds the proposed proprietary name, Pradaxa, acceptable for this product.

The proposed proprietary name must be re-reviewed 90 days before approval of the NDA. Additionally, if any of the proposed product characteristics as stated in this review are altered, DMEPA rescinds this finding and the name must be resubmitted for review. The conclusions upon re-review are subject to change.

1 BACKGROUND

1.1 INTRODUCTION

This review is written in response to a request from Boehringer Ingelheim Pharmaceuticals, Inc. for an assessment of the proposed proprietary name, Pradaxa, regarding potential name confusion with other proprietary or established drug names in the usual practice settings.

Additionally, container labels and carton labeling were provided for review and comment and will be reviewed in a separate review.

1.2 REGULATORY HISTORY

DMEPA found the proprietary name, Pradaxa, acceptable in the IND phase (OSE Review #2006-938 dated September 21, 2007).

1.3 PRODUCT INFORMATION

Pradaxa (dabigatran etexilate) is a direct thrombin inhibitor indicated for the prevention of stroke and systemic embolism in patients with atrial fibrillation and the reduction of vascular mortality in patients with atrial fibrillation. The recommended dose is 150 mg taken orally twice daily and 110 mg take orally twice daily for high bleeding risk patients. Pradaxa is available in 110 mg and 150 mg capsules. Pradaxa will be supplied in unit of use bottles of 60 capsules and blister packages containing (b)(4) and 60 capsules (10 x 6-capsule blister cards).

2 METHODS AND MATERIALS

Appendix A describes the general methods and materials used by the Division of Medication Error Prevention and Analysis (DMEPA) when conducting a proprietary name risk assessment for all proprietary names. Sections 2.1 and 2.2 identify specific information associated with the methodology for the proposed proprietary name, Pradaxa.

2.1 SEARCH CRITERIA

The DMEPA staff 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.^{1,2}

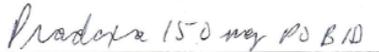
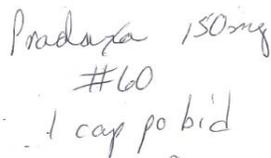
To identify drug names that may look similar to Pradaxa, the DMEPA staff also consider the orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (seven letters), upstrokes (two, capital letter ‘P’ and lower case letter ‘d’); downstrokes (none), cross-strokes (one, ‘x’), and dotted letters (none). Additionally, several letters in Pradaxa may be vulnerable to ambiguity when scripted, including the letter ‘P’ may appear as ‘B’, ‘D’ or ‘R’; lower case ‘r’ may appear as ‘e’, ‘v’ or ‘i’; lower case ‘a’ may appear as any of the vowels; lower case ‘d’ may appear as lower case ‘l’; and lower case ‘x’ may appear as lower case lower case ‘t’. As such, the DMEPA staff also considers these alternate appearances when identifying drug names that may look similar to Pradaxa.

When searching to identify potential names that may sound similar to Pradaxa, DMEPA staff searches for names with similar number of syllables (three), stresses (pra-DAX-a, PRA-dax-a, pra-dax-A), and placement of vowel and consonant sounds. Additionally, several letters in Pradaxa may be vulnerable to misinterpretation when spoken, including ‘Pr’ may be interpreted as ‘Br’; ‘x’ may be interpreted as ‘c’; and ‘a’ may be interpreted as ‘e,’ ‘i,’ or ‘o’. As such, the staff also considers these alternate pronunciations when identifying drug names that may sound similar to Pradaxa. The Applicant’s intended pronunciation of the proprietary name (pra dax’ a) was provided and taken into consideration.

2.2 FDA PRESCRIPTION ANALYSIS STUDIES

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, the following inpatient medication order, outpatient and verbal prescription was communicated during the FDA prescription studies.

Figure 1. Pradaxa Rx Study (conducted on November 30, 2009)

| HANDWRITTEN REQUISITION MEDICATION ORDER | VERBAL PRESCRIPTION |
|--|---|
| <p><u>Inpatient Medication Order :</u></p>  | <p>Pradaxa 150 mg #60 Take 1 capsule PO BID</p> |
| <p><u>Outpatient Prescription:</u></p>  | |

¹ Institute for Safe Medication Practices. Confused Drug name List (1996-2006). Available at <http://www.ismp.org/Tools/confuseddrugnames.pdf>

² Kondrack, G and Dorr, B. Automatic Identification of Confusable Drug Names. Artificial Intelligence in Medicine (2005)

3 RESULTS

3.1 DATABASE AND INFORMATION SOURCES

The searches yielded a total of 22 names as having some similarity to the name, Pradaxa.

Thirteen of the 22 names were thought to look like Pradaxa. These names are Pentoxil, Peridex, Permax, Posurdex^{***}, Pralidoxime, Prandin, Precedex, Prednisone, Prehist D, Prilosec, Prolixin, (b) (4), and Prolix. Four of the 22 names (Paxil, Pramoxin, Prestara, and Primaxin) were thought to sound like Pradaxa: Five of the 22 names (Pradax, Pradex, Prenexa, Prodroxy, and Prudoxin) were thought to both look and sound like Pradaxa.

DMEPA staff did not identify any United States Adopted Names (USAN) stems in the proposed proprietary name, as of January 4, 2010.

3.2 EXPERT PANEL DISCUSSION

The Expert Panel reviewed the pool of names identified by DMEPA staff (See Section 3.1 above) and noted one additional name (Ridaura) thought to have orthographic similarity to Pradaxa.

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

3.3 FDA PRESCRIPTION ANALYSIS STUDIES

A total of 24 practitioners responded to the prescription analysis studies, but none of the responses overlapped with any existing or proposed drug names. Ten respondents interpreted the name correctly as Pradaxa. The remainder of the respondents (n=14) misinterpreted the drug name, primarily because 'a' was misinterpreted as 'o,' 'e' or 'i' in the verbal and written studies. See Appendix B for the complete listing of interpretations from the verbal and written prescription studies.

3.4 COMMENTS FROM THE REVIEW DIVISION

3.4.1 Initial Phase of Review

In response to the OSE November 30, 2009 e-mail, the Division of Cardiovascular and Renal Products (DCRP) did not object to the proposed proprietary name, Pradaxa.

3.4.2 Midpoint of Review

On January 20, 2010, DMEPA notified DCRP via e-mail that we had no objections to the proposed proprietary name, Pradaxa. Per e-mail correspondence from DCRP on January 28, 2010, they indicated that they concur with our assessment of the proposed proprietary name, Pradaxa.

3.5 SAFETY EVALUATOR RISK ASSESSMENT

Independent searches by the primary Safety Evaluator resulted in five additional names, Didrex, Prasugrel (proprietary name: Effient), Plavix, Pletal, and Predair, thought to look similar to Pradaxa and represent a potential source of drug name confusion.

During review of the names identified in the databases, one of the names (Prolix) was noted to be not found in any of the commonly referenced databases and two of the names, Pradax (Canada) and Pradex (Mexico), are foreign products. Therefore, these three names were eliminated from further analysis.

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Thus, we evaluated a total of 25 names for their similarity to the proposed name.

4 DISCUSSION

Neither DDMAC nor the Division of Cardiovascular and Renal Products (DCRP) had concerns with the proposed name, Pradaxa.

DMEPA did not identify any aspects of the proposed proprietary name that could be a potential source of confusion other than the names with similar appearance and sounds to Pradaxa. DMEPA identified and evaluated 25 names for their potential similarity to the proposed name. Eleven names lacked orthographic and/or phonetic similarity and were not evaluated further (see Appendix C). Failure mode and effect analysis (FMEA) was then applied to determine if the proposed proprietary name could potentially be confused with the remaining 14 names and lead to medication errors. This analysis determined that the name similarity between Pradaxa was unlikely to result in medication errors with any of the 14 names for the reasons presented in Appendices D through G. Thus, DMEPA has no objection to the proprietary name, Pradaxa.

5 CONCLUSIONS AND RECOMMENDATIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Pradaxa, is not vulnerable to name confusion that could lead to medication errors nor was the name considered promotional. Thus, the Division of Medication Error Prevention and Analysis (DMEPA) has no objection to the proprietary name, Pradaxa, for this product at this time.

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.

The proposed proprietary name must be re-reviewed 90 days before approval of the NDA. If you have further questions or need clarifications, please contact Nina Ton, OSE Project Manager, at 301-796-1648.

5.1 COMMENTS TO THE APPLICANT

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

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

REFERENCES

1. *Micromedex Integrated Index* (<http://csi.micromedex.com>)

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

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

POCA is a database which was created for the Division of Medication Error Prevention and Analysis, FDA. 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.

3. *Drug Facts and Comparisons, online version, St. Louis, MO* (<http://factsandcomparisons.com>)

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

4. *FDA Document Archiving, Reporting & Regulatory Tracking System [DARRTS]*

DARRTS is a government database used to organize Applicant and Sponsor submissions as well as to store and organize assignments, reviews, and communications from the review divisions.

5. *Division of Medication Errors Prevention and Analysis proprietary name consultation requests*

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis 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](#), [generic drugs](#), [therapeutic biological products](#), [prescription](#) and [over-the-counter](#) human drugs and [discontinued drugs](#) and “[Chemical Type 6](#)” approvals.

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

The FDA Orange Book provides a compilation of approved drug products with therapeutic equivalence evaluations.

8. *U.S. Patent and Trademark Office* (<http://www.uspto.gov>)

USPTO provides information regarding patent and trademarks.

9. *Clinical Pharmacology Online* (www.clinicalpharmacology-ip.com)

Clinical Pharmacology contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common, combination, nutraceutical and nutritional products. It also 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 trade names that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

11. Natural Medicines Comprehensive Databases (www.naturaldatabase.com)

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

12. Stat!Ref (www.statref.com)

Stat!Ref contains full-text information from approximately 30 texts; it 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>)

USAN Stems List contains all the recognized USAN stems.

14. Red Book Pharmacy's Fundamental Reference

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

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

Lexi-Comp is a web-based searchable version of the Drug Information Handbook.

16. Medical Abbreviations Book

Medical Abbreviations Book contains commonly used medical abbreviations and their definitions.

APPENDICES

Appendix A:

FDA's Proprietary Name Risk Assessment considers the potential for confusion between the proposed proprietary name 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 Center. DMEPA 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.³

For the proposed proprietary name, DMEPA staff search a standard set of databases and information sources to identify names with orthographic and phonetic similarity and hold a Center for Drug Evaluation and Research (CDER) Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name. DMEPA staff also conducts internal CDER prescription analysis studies. When provided, DMEPA considers external prescription analysis study results and incorporate into the overall risk assessment.

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. DMEPA bases

³ National Coordinating Council for Medication Error Reporting and Prevention. <http://www.nccmerp.org/aboutMedErrors.html>. Last accessed 10/11/2007.

the overall risk assessment on the findings of a Failure Mode and Effects Analysis (FMEA) of the proprietary name, and focuses on the avoidance of medication errors.

FMEA is a systematic tool for evaluating a process and identifying where and how it might fail.⁴ DMEPA uses FMEA to analyze whether the drug names identified with orthographic or phonetic similarity to the proposed proprietary name could cause confusion that subsequently leads to medication errors in the clinical setting. DMEPA uses the clinical expertise of its staff to anticipate the conditions of the clinical setting where the product is likely to be used 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. Accordingly, the DMEPA staff considers the product characteristics associated with the proposed drug throughout the risk assessment because 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 proprietary name include, but are not limited to; established name of the proposed product, proposed indication of use, 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, DMEPA staff 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.⁵ DMEPA provides the product characteristics considered for this review in section one.

The Division of Medication Error Prevention and Analysis considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. DMEPA also compares 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 staff also examines 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 even dissimilarly spelled drug name pairs to appear very similar to one another. The similar appearance of drug names when scripted has led to medication errors. The DMEPA staff applies expertise gained from root-cause analysis of such medication errors to identify sources of ambiguity within the name that could be introduced when scripting (e.g., “T” may look like “F,” lower case ‘a’ looks like a lower case ‘u,’ etc). Additionally, other orthographic attributes that determine the overall appearance of the drug name when scripted (see Table 1 below for details). In addition, the DMEPA staff compares the pronunciation of the proposed proprietary name with the pronunciation of other drug names because verbal communication of medication names is common in clinical settings. If provided, DMEPA will consider the Sponsor’s intended pronunciation of the proprietary name. However, DMEPA also considers a variety of pronunciations that could occur in the English language because the Sponsor has little control over how the name will be spoken in clinical practice.

⁴ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

⁵ Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

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 | | |
|--------------------|---|---|---|
| | <i>Potential causes of drug name similarity</i> | <i>Attributes examined to identify similar drug names</i> | <i>Potential Effects</i> |
| Look-alike | Similar spelling | Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics | <ul style="list-style-type: none"> 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 Down strokes Cross-strokes Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics | <ul style="list-style-type: none"> Names may look similar when scripted, and lead to drug name confusion in written communication |
| 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 | <ul style="list-style-type: none"> Names may sound similar when pronounced and lead to drug name confusion in verbal communication |

Lastly, the DMEPA staff also considers the potential for the proposed proprietary 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. Consequently, DMEPA considers and evaluates these broader safety implications of the name throughout this assessment and the medication error staff provides additional comments related to the safety of the proposed proprietary name or product based on professional experience with medication errors.

1. Database and Information Sources

DMEPA staff conducts searches 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 the proposed proprietary name using the criteria outlined in Section 2.1. Section 6 provides a standard description of the databases used in the searches. To complement the process, the DMEPA staff 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, the DMEPA staff review the USAN stem list to determine if any USAN stems are present within the proprietary name. The individual findings of multiple safety evaluators are pooled and presented to the CDER Expert Panel.

2. CDER Expert Panel Discussion

DMEPA conducts an Expert Panel Discussion to gather CDER professional opinions on the safety of the proposed product and the proposed proprietary name. The Expert Panel is composed of Division of Medication Errors Prevention (DMEPA) staff and representatives from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The Expert Panel also discusses potential concerns regarding drug marketing and promotion related to the proposed names.

The primary Safety Evaluator presents the pooled results of the DMEPA staff 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 primary Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name.

3. 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 the proposed proprietary name 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 healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, inpatient medication orders and/or outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These orders are optically scanned and one prescription is delivered to a random sample of the 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.

4. Comments from the OND Review Division

DMEPA requests the Office of New Drugs (OND) responsible for the application for its 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. The primary Safety Evaluator addresses any comments or concerns in the Safety Evaluator's assessment.

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

5. External Proprietary Name Risk Assessment

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 the overall risk assessment to the findings of the proprietary name risk

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

6. Safety Evaluator Risk Assessment of the Proposed Proprietary Name

The primary Safety Evaluator applies his/her individual expertise gained from evaluating medication errors reported to FDA, conducts a Failure Mode and Effects Analysis, and provides an overall risk assessment 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 proprietary name to be confused with another drug name because of name confusion and, thereby, 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 orthographically or phonetically similar drug names prior to approval, where actions to overcome these issues are easier and more effective than remedies available in the post-approval phase.

In order to perform an FMEA of the proposed name, the primary Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product is has not been marketed, the primary Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product characteristics listed in Section one. 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 Discussion, and prescription studies, external studies, and identifies potential failure modes by asking:

“Is the proposed proprietary name 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 the proposed proprietary name 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 possess similarity that would cause confusion at any point in the medication use system, thus the name is eliminated from further review.

In the second stage of the Risk Assessment, the primary Safety Evaluator evaluates all potential failure modes 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 not ultimately be a source of medication errors in the usual practice setting, the primary Safety Evaluator eliminates the name 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 the use of an alternate proprietary name.

DMEPA will object to the use of proposed proprietary name when the primary Safety Evaluator identifies one or more of the following conditions in the Risk Assessment:

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

- a. 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 PROPRIETARY name or otherwise [21 U.S.C 321(n); See also 21 U.S.C. 352(a) & (n)].
- b. 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)].
- c. FMEA identifies the potential for confusion between the proposed proprietary name and other proprietary or established drug name(s), and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.
- d. The proposed proprietary name contains an USAN (United States Adopted Names) stem.
- e. DMEPA identifies a potential source of medication error within the proposed proprietary name. For example, 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 and another drug product.

If DMEPA objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the primary Safety Evaluator uses the FMEA process to identify strategies to reduce the risk of medication errors. DMEPA is likely to recommend that the Sponsor 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. In that instance, DMEPA may be able to provide the Sponsor with recommendations that reduce or eliminate the potential for error and, thereby, would render the proposed name acceptable.

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, DMEPA will provide a contingency objection based on the date of approval. Whichever product, the Agency approves first has the right to use the proprietary name, while DMEPA will recommend that the second product to reach approval seek an alternative name.

The threshold set for objection to the proposed proprietary name may seem low to the Sponsor. However, the safety concerns set forth in criteria a through e are supported either by FDA regulation or by external healthcare authorities, including the Institute of Medicine (IOM), World Health Organization (WHO), the Joint Commission, and the Institute for Safe Medication Practices (ISMP). These organizations have examined medication errors resulting from look- or sound-alike drug names and called for regulatory authorities to address the issue prior to approval. Additionally, DMEPA contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and a preventable source of medication error that, in many instances, the Agency and/or Sponsor can identify and rectify prior to approval to avoid patient harm.

Furthermore, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to rectify post-approval. Educational and other post-approval efforts are low-leverage strategies that have had limited effectiveness at alleviating medication errors involving drug name confusion. Sponsors have undertaken higher-leverage strategies, such as drug name changes, in the past but at great financial cost to the Sponsor and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for approving the error-prone proprietary name. Moreover, even after Sponsors' have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioners' vocabulary, and as a result, 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.

Appendix B: FDA Prescription Study Responses (conducted November 30, 2009).

| Written Outpatient | Written Inpatient | Verbal Prescription |
|--------------------|-------------------|---------------------|
| Pradaxa | Pradaxa | Prodaxa |
| Pradaxa | Pradexo | Prodaxa |
| Pradaxa | Pradoxaxa | Prodaxa |
| Pradaxa | Pradaxa | Pridaxa |
| Pradaxa | Pradoxaxa | Pradaxa |
| Pradoxaxa | Pradoxaxa | |
| Pradoxaxa | Pradoxaxa | |
| | Pradaxa | |
| | Pradoxaxa | |

Appendix C: Names Lacking Orthographic and/or Phonetic Similarity.

| Name | Similarity to Pradaxa |
|-------------|-----------------------|
| Paxil | Sound |
| Pentoxil | Look |
| Permax | Look |
| Plavix | Look |
| Pletal | Look |
| Pralidoxime | Look |
| Pramoxin | Sound |
| Prednisone | Look |
| Prehist D | Look |
| Prilosec | Look |
| Primaxin | Sound |

Appendix D: Products marketed under a different proprietary name

| Proprietary Name | Similarity to Pradaxa | Reason for Discard |
|------------------|-----------------------|----------------------------------|
| (b) (4) | Look | Approved under the name, Olux E |
| Posurdex*** | Look | Approved under the name, Ozurdex |

Appendix E: Products with no overlap in strength or dose.

| Product name with potential for confusion | Similarity to Pradaxa | Dosage Form/ Strength | Usual Dose |
|--|-----------------------|---|---|
| Pradaxa (Dabigatran Etexilate) | N/A | Capsule: 110 mg, 150 mg | 150 mg orally twice daily |
| Prandin (Repaglinide) | Look | Tablet: 0.5 mg, 1 mg, 2 mg | Individualized dosing Starting dose: 0.5 mg with each meal |
| Prasugrel (established name for Effient) | Look | Tablet: 5 mg, 10 mg | ≥ 60 kg: 10 mg orally once daily < 60 kg: 5 mg orally once daily |
| Prestara (Prasterone) <i>*Not currently approved; Product not found in commonly referenced sources</i> | Sound | Tablet: 25 mg | 200 mg orally once daily |
| Prudoxin (Doxepin Hydrochloride) | Look and Sound | Topical cream: 5% | Apply to affected area four times daily |
| Prodroxy (Medroxyprogesterone Acetate) | Look and Sound | Not available in commonly referenced databases. Medroxyprogesterone acetate oral tablet strengths: 2.5 mg, 5 mg, 10 mg | Specific dosing information not available in commonly referenced databases Medroxyprogesterone acetate dose: 5 mg to 10 mg orally once daily |

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

| | | | |
|---|------|---|--|
| <p>Prolixin (Fluphenazine Hydrochloride) <i>*Discontinued (generics available)</i></p> <p>Prolixin Enanthate (Fluphenazine Enanthate) <i>* Discontinued (no generics available)</i></p> | Look | <p>Prolixin: Tablet: 1 mg, 2.5 mg, 5 mg, 10 mg Oral elixir: 2.5 mg/5 mL Oral concentrate: 5 mg/mL Injectable: 2.5 mg/mL</p> <p>Prolixin Enanthate: Injectable: 25 mg/mL</p> | <p>Prolixin: Oral: <i>Starting dose:</i> 2.5 mg to 10 mg/day in divided doses at 6 to 8 hour intervals <i>Maintenance dose:</i> 1 mg or 5 mg once daily</p> <p>Injectable: Starting dose: 1.25 mg (0.5 mL) intramuscularly; Total daily dose may range from 2.5 mg to 10 mg in divided doses at 6 to 8 hour intervals</p> <p>Prolixin Enanthate: Information not available</p> |
| <p>Prenexa (Prenatal vitamin)</p> | Look | Capsule | 1 capsule orally daily |
| <p>Predair (Prednisolone Sodium Phosphate) <i>*Discontinued branded generic (Other generics available)</i></p> | Look | Ophthalmic Solution: 0.11% | Instill 1 or 2 drops of solution into the conjunctival sac up to every hour during the day and every 2 hours during the night |

Appendix F: Products with numerical similar or achievable dose with differentiating product characteristics

| Product name with potential for confusion | Similarity to Pradaxa | Dosage Form/ Strength | Usual Dose (if applicable) | Differentiating Product Characteristics |
|--|-----------------------|--------------------------------|--|--|
| <p>Pradaxa (Dabigatran Etexilate)</p> | N/A | Capsule: 110 mg, 150 mg | 150 mg (one capsule) orally twice daily | N/A |
| <p>Peridex (Chlorhexidine Gluconate)</p> | Look | Dental solution: 0.12% | Rinse orally 15 mL (1 capful) for 30 seconds twice daily | Strength (Pradaxa requires strength on prescription orders which will differentiate the two products); dosage form |

| | | | | |
|--|------|--------------------------|--|--|
| Precedex (Dexmedetomidine) | Look | Injection: 100 mcg/mL | Loading dose: 1 mcg/kg over 10 min Maintenance dose: 0.2-0.7 mcg/kg/hr | Route of administration, dosage form, frequency of administration, strength |
| Prolixin Decanoate (Fluphenazine Decanoate) <i>*Discontinued (generics available)</i> | Look | Injectable: 25 mg/mL | Individualized to patient. <i>Starting dose:</i> 12.5 to 25 mg intramuscularly or subcutaneously <i>Maximum dose:</i> 100 mg/dose | Route of administration, dosage form, strength, frequency of administration |
| Ridaura (Auranofin) | Look | Capsule: 3 mg | 6 mg/day either as 3 mg (1 capsule) twice daily orally or 6 mg (2 capsules) daily orally | Strength (Pradaxa requires strength on prescription orders which will differentiate the two products) |

Appendix G: Products with numerical overlap in strength or achievable dose.

| Failure Mode: Name confusion | Causes (could be multiple) | Effects |
|---|--|---|
| Pradaxa (Dabigatran Etexilate) | Capsule: 110 mg, 150 mg | 150 mg (one capsule) orally twice daily |
| Didrex (Benzphetamine Hydrochloride) Tablet: 50 mg | Orthographic similarity: ‘D’ and ‘P’ can appear similar; overlapping letters ‘d’ and ‘x’; upstroke of lower case ‘d’ Overlapping frequency (twice daily), dosage form (tablet vs. capsule) and route of administration (oral) Numerical overlap in strength (50 mg vs. 150 mg) | The orthographic differences in the names help to minimize the risk of medication errors in the usual practice setting. <i>Rationale:</i> Although the first letter of the names (‘D’ and ‘P’) may look similar especially when scripted, the name pair only overlap in 2 letters (lower case ‘d’ and ‘x’) and differ in the remaining letters (4 letters vs. 5 letters). The difference in the majority of the letters in the names and the difference of the ending (‘x’ vs. ‘a’) may help in differentiating the two names. |

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|-------------------------|------------------------|--|--|
| NDA-22512 | ORIG-1 | BOEHRINGER INGELHEIM PHARMACEUTICA LS INC | PRADAXA (DABIGATRAN ETEXILATE MESYLATE) |

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

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