

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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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**

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Through: Carol Holquist, RPh, Division Director
Division of Medication Error Prevention and Analysis
(DMEPA)

From: Denise V. Baugh, PharmD, BCPS, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Proprietary Name Review

Drug Name and Strengths, Application Types/Numbers: Xarelto (Rivaroxaban) Tablets
10 mg
NDA 022406 (Division of Hematology Products)

Xarelto (Rivaroxaban) Tablets
(b) (4) 20 mg
NDA 202439 (Division of Cardio-Renal Products)

Applicant: Johnson & Johnson Pharmaceutical Research &
Development, LLC on behalf of Ortho-McNeil-Janssen-
Pharmaceuticals, Inc.

OSE RCM #: 2011-512
2011-437

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

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EXECUTIVE SUMMARY

This review summarizes DMEPA's evaluation of the proposed proprietary name, Xarelto for Rivaroxaban Tablets. 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, Xarelto, acceptable for this product. DMEPA will notify the Applicant of these findings via letter

1 BACKGROUND

1.1 INTRODUCTION

This review responds to a request received from Johnson & Johnson Pharmaceutical Research & Development, LLC on behalf of Ortho-McNeil-Janssen-Pharmaceuticals, Inc., submitted February 18, 2011, to evaluate the proposed proprietary name, Xarelto, regarding promotional concerns and potential name confusion with other proprietary or established drug names based on the product characteristics provided by the Applicant.

The Applicant also submitted container labels and carton labeling which will be reviewed under separate cover (OSE Review #2011-438 and #2011-513).

1.2 REGULATORY HISTORY

Rivaroxaban is the established name for the proposed proprietary name, Xarelto, previously found acceptable by DMEPA (OSE Review # 2007-1832 dated April 30, 2009) under IND# 64,892. At that time the dose was 10 mg taken orally once daily and the indication was for the prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing hip replacement or knee replacement surgery. No other indication or treatment regimen was proposed at that time.

1.3 PRODUCT INFORMATION

Xarelto is a new molecular entity which will have two different indications and corresponding treatment regimens. Details are described below.

1.3.1 Prophylaxis of Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE)

Xarelto (Rivaroxaban Tablets) is indicated for the prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing hip replacement or knee replacement surgery. The recommended oral dose is 10 mg taken once daily with or without food. The initial dose should be taken at least 6 to 10 hours after surgery once hemostasis has been established. Xarelto should be used with caution in patients with CrCl 15 mL/minute to less than 30 mL/minute. It is not recommended in patients with CrCl less than 15 mL/minute. The treatment duration is 35 days (hip surgery) to 14 days (knee surgery). Xarelto will be supplied in bottles of 30 and in a (b) (4) carton containing 10 blister cards of 10 tablets each.

1.3.2 Prevention of Stroke and Systemic Embolism

Xarelto (Rivaroxaban Tablets) is indicated for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation. (b) (4)

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, Xarelto.

2.1 SEARCH CRITERIA

For this review, particular consideration was given to drug names beginning with the letter ‘X’ 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 ‘Xarelto’, the DMEPA staff also considers 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 (three, upper case ‘X’, lower case ‘l’ and ‘t’), down-strokes (none), cross-strokes (two, upper case ‘X’ and lower case ‘t’) and dotted letters (none). Additionally, several letters in Xarelto may be vulnerable to ambiguity when scripted (see Appendix B). As such, the DMEPA staff also considers these alternate appearances when identifying drug names that may look similar to Xarelto.

When searching to identify potential names that may sound similar to Xarelto, the DMEPA staff searches for names with similar number of syllables (three), stresses (XA-rel-to, xa-REL-to, or za-rel-TO), and placement of vowel and consonant sounds. Additionally, the DMEPA staff considers that pronunciation of parts of the name can vary, such as the letter ‘x’ which may be interpreted as ‘z’ and the letters ‘to’ may be interpreted as ‘tow’.

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

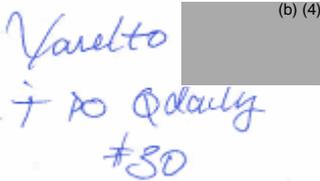
² Kondrack, G and Dorr, B. Automatic Identification of Confusable Drug Names. Artificial Intelligence in Medicine (2005)

The Applicant's intended pronunciation (zah-REL-toe) was also taken into consideration, as it was included in the Proprietary Name Review Request. However, names are often mispronounced and/or spoken with regional accents and dialects, so other potential pronunciations of the name are considered.

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 prescriptions were communicated during the FDA prescription studies.

Figure 1. Xarelto Prescription Study (conducted on April 26, 2011)

HANDWRITTEN PRESCRIPTION and MEDICATION ORDER	VERBAL PRESCRIPTION
<p><u>Inpatient Prescription:</u></p> 	<p>"Xarelto 10 mg orally daily"</p>
<p><u>Outpatient Prescription:</u></p> 	

3 RESULTS

The following sections describe DMEPA's findings from the database searches, CDER Expert Panel Discussion, and FDA prescription analysis studies.

3.1 DATA BASE AND INFORMATION SOURCES

The DMEPA safety evaluator searches yielded a total of 20 names as having some similarity to the proposed proprietary name Xarelto.

Sixteen of the 20 names (Kalbitor, Kaletra, Kariva, Parafon Forte DSC, Ramelteon, Varicella, Verdeso, Vivella Dot, Voltaren, Xalatan, (b) (4), Xeroflo, Xiaflex***, Xodol, Zarelix, and Zometa) were thought to look like Xarelto. One name (Zarontin) was thought to sound like Xarelto and three names Lorelco, Xarelto, and Xeloda were thought to look and sound like Xarelto.

A search of the United States Adopted Name stem list on April 26, 2011, did not identify any United States Adopted Names (USAN) stem within the proposed name, Xarelto.

3.2 CDER EXPERT PANEL DISCUSSION

The Expert Panel reviewed the pool of names identified by DMEPA safety evaluators (See Section 3.1 above) and did not identify additional names which were thought to have phonetic or orthographic similarity to Xarelto.

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

3.3 FDA PRESCRIPTION ANALYSIS STUDIES

A total of 41 practitioners responded and none of the names overlapped with existing names. Twenty-five (n = 25) of the participants interpreted the name correctly as 'Xarelto' with correct interpretation occurring in the inpatient (n = 10), outpatient (n = 13), and verbal studies (n = 2). The remainder of the responses misinterpreted the drug name. Common misinterpretations included mistaking the first letter 'X' for the letter 'C', 'S' or 'Z' and the lower case 'a' for 'e', 'y', 'o' or 'u'. See Appendix C for the complete listing of interpretations from the verbal and written prescription studies.

3.4 COMMENTS FROM THE DIVISION OF HEMATOLOGY PRODUCTS (DHP)

3.4.1 Initial Phase of Review

In response to the OSE March 3, 2011, e-mail, the Division of Hematology Products stated that they concur with DDMAC.

3.4.2 Midpoint of Review

On May 9, 2011, DMEPA notified DHP via e-mail that we find the name, Xarelto, acceptable. Per e-mail correspondence from DHP on May 12, 2011, they "had no objections" to Xarelto.

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

3.5 COMMENTS FROM THE DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

3.5.1 Initial Phase of Review

In response to the OSE March 3, 2011, e-mail, the Division of Cardiovascular and Renal Products (DCRP) stated that they had no objections to the proposed name, Xarelto.

3.5.2 Midpoint of Review

On May 9, 2011, DMEPA notified DCRP via e-mail that we find the name, Xarelto, acceptable. Per e-mail correspondence from DCRP on May 9, 2011, they “have no objections to Xarelto”.

3.6 SAFETY EVALUATOR RISK ASSESSMENT

The primary safety evaluator performed an independent search for names that would represent a potential source of drug name confusion. Additionally, although there were five names (Kaletra, Kariva, Xeroflo, Lorelco, and Zarontin) identified in our databases as well as in our previous review (OSE# 2009-637 dated April 30, 2009), we re-evaluated all the names for their potential for confusion as a result of the change in product characteristics for Xarelto. Furthermore, we considered the vulnerability to confusion that this name would pose if it were available as a single strength product (10 mg).

We identified four additional names (Zaditor, Xiral Zimulti***, (b) (4)) thought to look similar to Xarelto and represent a potential source of drug name confusion.

As such, a total of 32 names were further analyzed to determine if the drug names could be confused with Xarelto and if the drug name confusion would likely result in a medication error in the usual practice setting. Thirteen names were identified in our previous review, fifteen *new* names were identified in our database search, and four were identified in our independent search.

4 DISCUSSION

The proposed name, Xarelto, was evaluated from a safety and promotional perspective based on the product characteristics provided by the Applicant. Furthermore, we sought input from pertinent disciplines involved with the review of this application and considered it accordingly.

4.1 PROMOTIONAL ASSESSMENT

DDMAC had no concerns regarding the proposed name from a promotional perspective, and did not offer any additional comments relating to the proposed name. The Division of Hematology Products, the Division of Cardiovascular Renal Products, and DMEPA concurred with the promotional assessment.

4.2 SAFETY ASSESSMENT

DMEPA identified 19 *new* names for their potential similarity to the proposed name, Xarelto. No other aspect of the name was identified as a potential source of confusion. Upon evaluation of the similar names, four of the 19 were eliminated from further consideration for the following reasons: two names lacked sufficient orthographic and/or phonetic similarity (Appendix D), one name was identified in our database search and found to be the subject of this review (Appendix E), and one name is a foreign name (Appendix F).

Failure mode and effects analysis (FMEA) was then applied to determine if the proposed proprietary name could potentially be confused with the remaining fifteen names and lead to medication errors. This analysis determined that the name similarity between Xarelto and the

identified names was unlikely to result in medication errors with all of the products identified for the reasons presented in Appendix G.

5 CONCLUSIONS AND RECOMMENDATIONS

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

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.

If you have further questions or need clarifications, please contact Sue Kang, OSE Project Manager for the Division of Hematology Products, at 301-796-4216 or Nina Ton, OSE Project Manager for the Division of Cardiovascular and Renal Products, at 301-796-1648.

6 PRIOR OSE REVIEW

OSE Review# 2009-637. *DMEPA Proprietary Name Review for Xarelto (Rivaroxaban) Tablets 10 mg*, Tselaine Jones Smith; April 30, 2009.

7 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 Applicant 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 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,

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

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

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 Applicant’s intended pronunciation of the proprietary name. However, DMEPA also considers a variety of pronunciations that could occur in the English language because the Applicant has little control over how the name will be spoken in clinical practice.

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	<ul style="list-style-type: none"> Names may look similar when scripted, and lead to drug name confusion in written communication

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

		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	<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. 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

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

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:

- 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 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. In that instance, DMEPA may be able to provide the Applicant 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 Applicant. 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), Joint Commission on Accreditation of Hospitals (JCOAH), 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 Applicant 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. Applicants have undertaken higher-leverage strategies, such as drug name changes, 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 approving the error-prone proprietary name. Moreover, even after Applicants' 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. (See Section 4 for limitations of the process).

Appendix B: Letters with possible orthographic or phonetic misinterpretation

Letters in proposed name, Xarelto	Scripted may appear as	Spoken may be interpreted as
Capital 'X'	K, P, Z, V, Y	Z, S, C
lower case 'a'	el, ci, cl, d, o, u	Any vowel
lower case 'r'	s, n, e, v	
lower case 'e'	a, i, l, p	Any vowel
lower case 'l'	b, e, s, i	
Lower case 't'	f, r, x, a	d
Lower case 'o'	a, c, e, u	oh

Appendix C: FDA Prescription Study Responses for Saflutan (conducted April 26, 2011)

Inpatient Medication Order	Outpatient Prescription	Voice Prescription
Xarleto	Xarelto	Xorelto
Xarllto	Xarelto	Xarelto
Tareeto	xarelto	serelto
Xarelto	xarelto	Cyrelto
Xarelto	Xarelto	Zarelto
Xarelto	Xarelto	Xarelto
Xarllto	Xarelto	Zorelto
Xarelto	xarelto	Surelto
Xarelto	xarelto	Ceralto
Xarelto	Xarelto	
Xarelto	Xarelto	
Xarelto	Xarelto	
Xareeto	Xarelto	
Xarelto	Xarelto	
xarelto		
Xarelto		
xarelto		
Xareeto		

Appendix D: Proprietary names that lack convincing orthographic and/or phonetic similarities

Proprietary Name	Similarity to Xarelto
Xeloda	Look and Sound
Parafon Forte DSC	Look

Appendix E: Drug name that is the subject of this review.

Proprietary Name	Source
Xarelto (granted approval in Europe September, 2008)	Micromedex, DARRTS, Facts & Comparisons

Appendix F: Drug name that is foreign and not likely to be confused with 'Xarelto'.

Proprietary Name	Comments
Zarelis (Venlafaxine Hydrochloride)	Marketed in Portugal (per Micromedex)

Appendix G: Potentially confusing names with orthographic and/or phonetic differences and differentiating product characteristics that decrease the risk of medication errors.

Failure Mode: Name confusion	Causes (could be multiple)	Rationale:
<p>Proposed name: Xarelto (Rivaroxaban) Tablet</p>	<p>Strength: 10 mg (b) (4) 20 mg</p>	<p>Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation: 20 mg once daily</p> <p>Prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing knee or hip replacement surgery: 10 mg once daily</p>
<p>Kalbitor (Ecallantide) Injection 10 mg/mL <i>Usual dose:</i> 30 mg (3 mL) given subcutaneously in three 10 mg (1 mL) injections. Repeat within a 24 hour period if symptoms persist.</p>	<p>Orthographic similarity stems from similar appearance of first letters (K vs. X) in some handwriting samples. Additionally, both names include two consecutive upstrokes within their names ('lb' vs. 'lt'). Numerical overlap in strength exists (10 mg) as well as the existence of achievable doses (two 10 mg doses = 20 mg and (b) (4))</p>	<p>The marketed name, 'Kalbitor', has one additional up stroke ('t') in its name which gives this name a different shape orthographically from the proposed name, 'Xarelto'. Additionally, the consecutive up strokes occur earlier in the name, 'Kalbitor', versus that of 'Xarelto' which occurs near the end of the name. These differences will likely distinguish this name pair from each other.</p> <p>Differing product characteristics include the dose (30 mg vs. 10 mg or 20 mg) and route of administration (subcutaneous vs. oral).</p> <p>Xarelto is available in more than one strength and therefore this information will need to be provided on a prescription to dispense/administer the drug as intended.</p>
<p>Ramelteon (active ingredient for the proprietary name, Rozerem) Tablet 8 mg <i>Usual dose:</i> One tablet taken within 30 minutes of going to bed.</p>	<p>Orthographic similarity stems from the similar appearance of their first letters ('R' vs. 'X') in some handwriting samples and the fact that both names share the letters '-elt-' in the same positions within their names.</p> <p>Overlapping product characteristics include route of administration (oral) and frequency of administration (daily).</p>	<p>The marketed name, Ramelteon, terminates with the letters '-on' giving this name a longer appearance and a different shape when compared to the proposed name, Xarelto. This feature may help to distinguish between this name pair.</p> <p>Xarelto is available in more than one strength and therefore this information will need to be provided on a prescription to dispense/administer the drug as intended.</p>

Failure Mode: Name confusion	Causes (could be multiple)	Rationale:
<p>Proposed name: Xarelto (Rivaroxaban) Tablet</p>	<p>Strength: 10 mg, (b) (4) 20 mg</p>	<p>Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation: 20 mg once daily</p> <p>Prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing knee or hip replacement surgery: 10 mg once daily</p>
<p>Verdeso (Desonide) Foam 0.05%</p> <p><i>Usual dose:</i> Apply a thin layer of foam to the affected area (s) twice daily.</p>	<p>Orthographic similarity stems from the similar appearance of their first letters ('V' vs. 'X') in some handwriting samples, the fact that both names have at least one up stroke, and that they both end with an 'o'.</p>	<p>The marketed name, Verdeso, has one up stroke in the middle of its name whereas the proposed name, Xarelto, has two consecutive up strokes near the end, giving these names different shapes. This difference may distinguish these names from each other.</p> <p>Differing product characteristics include strength (0.05% vs. 10 mg, 20 mg), route of administration (topical vs. oral), and frequency of administration (twice daily vs. once daily).</p> <p>Xarelto is available in more than one strength and therefore this information will need to be provided on a prescription to dispense/administer the drug as intended.</p>
<p>Varicella (the established name for a live vaccine) 1,350 PFU/0.5 mL</p> <p><i>Usual dose:</i> 0.5 mL given subcutaneously at an elected date and a second 0.5 mL dose 4 to 8 weeks later.</p>	<p>Orthographic similarity stems from the similar appearance of their first letters ('V' vs. 'X') in some handwriting samples, the fact that these names share the same second and third letters ('ar') and they both have consecutive up strokes ('ll' vs. 'lt') within their names.</p>	<p>The marketed name, Varicella, is longer in length than the proposed name, Xarelto. This feature may distinguish this name pair.</p> <p>Differences in product characteristics include dose (0.5 mL vs. 10 mg, 20 mg), route of administration (subcutaneous vs. oral), and frequency of administration (an injection 4 to 8 weeks apart vs. once daily).</p> <p>Xarelto is available in more than one strength and therefore this information will need to be provided on a prescription to dispense/administer the drug as intended.</p>

Failure Mode: Name confusion	Causes (could be multiple)	Rationale:
<p>Proposed name: Xarelto (Rivaroxaban) Tablet</p>	<p>Strength: 10 mg, (b) (4)</p>	<p>Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation: 20 mg once daily</p> <p>Prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing knee or hip replacement surgery: 10 mg once daily</p>
<p>Vivella Dot (Estradiol) Transdermal Patch</p> <p>0.025 mg/24 hr, 0.038 mg/24 hr, 0.05 mg/24 hr, 0.075 mg/24 hr, 0.1 mg/24 hr</p> <p><u>Usual dose:</u> Apply twice weekly.</p>	<p>Orthographic similarity stems from the similar appearance of their first letters ('V' vs. 'X') in some handwriting samples and the fact that they both have consecutive up strokes ('ll' vs. 'lt') within their names.</p>	<p>The marketed name, Vivella Dot, includes the modifier 'Dot' which makes this name longer in appearance than the proposed name, Xarelto. This feature will likely distinguish this name pair from each other.</p> <p>Differences in product characteristics include dose (0.025 mg/24 hr, 0.038 mg/24 hr, 0.05 mg/24 hr, 0.075 mg/24 hr, 0.1 mg/24 hr vs. 10 mg (b) (4)), route of administration (topical vs. oral), and frequency of administration (twice weekly vs. once daily).</p> <p>Xarelto and Vivella Dot are both available in more than one strength and therefore this information will need to be provided on a prescription to dispense/administer the drug as intended.</p>
<p>Voltaren (Diclofenac) Tablet</p> <p>25 mg, 50 mg, 75 mg</p> <p><u>Usual dose:</u> 50 mg three times daily</p>	<p>Orthographic similarity stems from similar appearance of their first letters ('V' vs. 'X') in some handwriting samples and the fact that both names share the letters '-lt-' within their names.</p> <p>Overlapping product characteristics include route of administration (oral).</p>	<p>The marketed name, Voltaren, has four letters beyond its consecutive up strokes, '-lt-'. This is in contrast to the proposed name, Xarelto, which has only one letter beyond the letters '-lt-'. This difference gives these names different shapes and may distinguish them from each other.</p> <p>One differing product characteristic includes the frequency of administration (three times daily vs. once daily).</p> <p>Xarelto and Vivella Dot are both available in more than one strength and therefore this information will need to be provided on a prescription to dispense/administer the drug as intended.</p>

Failure Mode: Name confusion	Causes (could be multiple)	Rationale:
<p>Proposed name: Xarelto (Rivaroxaban) Tablet</p>	<p>Strength: 10 mg, (b) (4) 20 mg</p>	<p>Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation: 20 mg once daily</p> <p>Prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing knee or hip replacement surgery: 10 mg once daily</p>
<p>Xalatan (Latanoprost) Ophthalmic Solution 0.005%</p> <p><u>Usual dose:</u> One drop in the affected eye(s) once daily in the evening.</p>	<p>Orthographic similarity stems from sharing the first two letters of their names ('Xa') and the fact that both names have the same up strokes ('l' and 't').</p> <p>One overlapping product characteristic is the frequency of administration (once daily).</p>	<p>Although this name pair share the same up strokes, the marketed name, Xala<u>l</u>an, contains solitary up strokes whereas those in the proposed name, Xare<u>l</u>to, are consecutive. The different locations of the letters give the names different shapes and may distinguish them from each other.</p> <p>Differing product characteristics include strength (0.005% vs. 10 mg, 20 mg) and route of administration (ocular vs. oral).</p> <p>Xarelto is available in more than one strength and therefore this information will need to be provided on a prescription to dispense/administer the drug as intended.</p>

(b) (4)

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

Failure Mode: Name confusion	Causes (could be multiple)	Rationale:
<p>Proposed name: Xarelto (Rivaroxaban) Tablet</p>	<p>Strength: 10 mg, (b) (4) 20 mg</p>	<p>Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation: 20 mg once daily</p> <p>Prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing knee or hip replacement surgery: 10 mg once daily</p>
<p>Xodol (Hydrocodone and Acetaminophen) Tablet</p> <p>10 mg/300 mg, 5 mg/300 mg, 7.5 mg/300 mg</p> <p><u>Usual dose:</u></p> <p>One tablet every 4 to 6 hours</p>	<p>Orthographic similarity stems from the fact that these names share the first letter ('X') in their names and both names have up strokes within their names ('d' and 'l' vs. 'l' and 't').</p>	<p>Although both names have up strokes, the marketed name, Xodol, contains solitary up strokes with one appearing at the end of the name whereas those in the proposed name, Xarelto, are consecutive. The different locations of the letters give the names different shapes and may distinguish them from each other.</p> <p>One differing product characteristic is the frequency of administration (every 4 to 6 hours vs. once daily).</p> <p>Xarelto and Xodol are both available in more than one strength and therefore this information will need to be provided on a prescription to dispense/administer the drug as intended.</p>
<p>Zometa (Zoledronic Acid) Injection</p> <p>4 mg/5 mL</p> <p><u>Usual dose:</u></p> <p>4 mg given intravenously over 15 to 30 minutes as a single dose or given every 3 to 4 weeks depending upon diagnosis</p>	<p>Orthographic similarity stems from the similar appearance of their first letters ('Z' vs 'X') in some handwriting samples and the fact that both names share the same cross stroke ('t') in a similar position within their names.</p>	<p>The proposed name, Zometa, contains a solitary cross stroke, 't', near the end of its name, whereas the proposed name, Xarelto, contains two consecutive up strokes. This difference may distinguish these names from each other.</p> <p>Differing product characteristics include dose (4 mg vs. 10 mg, 20 mg) and route of administration (intravenous vs. oral).</p> <p>Xarelto is available in more than one strength and therefore this information will need to be provided on a prescription to dispense/administer the drug as intended.</p>

Failure Mode: Name confusion	Causes (could be multiple)	Rationale:
<p>Proposed name: Xarelto (Rivaroxaban) Tablet</p>	<p>Strength: 10 mg, (b) (4) 20 mg</p>	<p>Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation: 20 mg once daily</p> <p>Prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing knee or hip replacement surgery: 10 mg once daily</p>
<p>Zaditor (Ketotifen) Ophthalmic Solution 0.025%</p> <p><u>Usual dose:</u> One drop in the affected eye(s) every 8 to 12 hours</p>	<p>Orthographic similarity stems from the similar appearance of their first letters ('Z' vs. 'X') in some handwriting samples and the fact that they share the letters 'a', 't', and 'o' in the same or similar positions.</p>	<p>Differing product characteristics include dose (one drop vs. 10 mg, 20 mg), route of administration (ocular vs. oral), and frequency of administration (every 8 to 12 hours vs. once daily).</p> <p>Xarelto is available in more than one strength and therefore this information will need to be provided on a prescription to dispense/administer the drug as intended.</p>
<p>Xiral (Chlorpheniramine and Methscopolamine and Pseudoephedrine) extended release oral tablet 8 mg/2.5 mg/120 mg</p> <p>NOTE: 'Xiral' is off the market but components of this combination product are still available</p> <p><u>Usual dose:</u> Varies, not to exceed 240 mg of pseudoephedrine and 24 mg of chlorpheniramine 24 hours</p>	<p>Orthographic similarity stems from sharing the same letters in the same positions within their names ('X', 'r', and 'l').</p> <p>Overlapping product characteristics include route of administration (oral).</p>	<p>The proposed name, Xarelto, has two letters at the end of its name giving it a different shape and longer appearance than the marketed name, Xiral. This difference may distinguish this name pair from each other.</p> <p>Differences in product characteristics include dose (one tablet vs. 10 mg or 20 mg).</p> <p>Xarelto is available in more than one strength and therefore this information will need to be provided on a prescription to dispense/administer the drug as intended.</p>

Failure Mode: Name confusion	Causes (could be multiple)	Rationale:
<p>Proposed name: Xarelto (Rivaroxaban) Tablet</p>	<p>Strength: 10 mg, (b) (4) 20 mg</p>	<p>Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation: 20 mg once daily</p> <p>Prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing knee or hip replacement surgery: 10 mg once daily</p>
<p>(b) (4) (Norethindrone and Ethinyl Estradiol and Ferrous Fumarate) Tablet 0.8 mg /0.025 mg <i>Usual dose:</i> One tablet orally once daily (Note: DMEPA objected to this name previously [OSE# 2010-929] and the product was approved without a proprietary name [NDA# 22573])</p>	<p>Orthographic similarity stems from the similar appearance of their first letters (b) (4) vs. 'X') in some handwriting samples, the fact that both names contain up strokes in the same position within their names, and both names are the same length.</p> <p>Overlapping product characteristics include route of administration (oral) and frequency of administration (once daily).</p>	<p>(b) (4)</p> <p>Xarelto is available in more than one strength and therefore this information will need to be provided on a prescription to dispense/administer the drug as intended.</p>
<p>Zimulti*** (Rimonabant) Tablets 20 mg <i>Usual dose:</i> One tablet every morning before breakfast. (NOTE: The Applicant withdrew the unapproved NDA from consideration by the Agency as of June 29, 2007)</p>	<p>Orthographic similarity stems from the similar appearance of their first letters ('Z' vs. 'X') in some handwriting samples, the fact that both names contain the same up strokes in the same position within their names, and both names are the same length.</p> <p>Overlapping product characteristics include strength (20 mg), route of administration (oral) and frequency of administration (once daily)</p>	<p>The name Zimulti*** contains the letter 'm' which is distinguishable by its double hump appearance. Additionally, the terminal letter for Xarelto is an 'o' appears different in this position than the letter 'i' which is the last letter in Zimulti***. These differences may help to distinguish this name pair.</p> <p>Xarelto is available (b) (4) and therefore this information will need to be provided on a prescription to dispense/administer the drug as intended.</p>

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

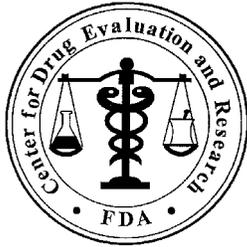
Failure Mode: Name confusion	Causes (could be multiple)	Rationale:
Proposed name: Xarelto (Rivaroxaban) Tablet	Strength: 10 mg, (b) (4), 20 mg	Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation: 20 mg once daily Prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing knee or hip replacement surgery: 10 mg once daily
Xiaflex (Collagenase Clostridium) Injection 0.9 mg <u>Usual dose:</u> Inject 0.58 mg into a palpable Dupuytren's cord according to the injection procedure; may repeat up to three times per cord at 4 week intervals	Orthographic similarity stems from sharing the same first letters ('X') and the fact that both names have consecutive up strokes in their names ('fl' vs. 'lt).	The consecutive up stroke in the name, Xiaflex occurs in the fourth and fifth position whereas they are present in the fifth and sixth position. Additionally, the name 'Xiaflex' ends with a cross stroke, ('x') which distinguishes this from the last letter ('o') in the proposed name, Xarelto. Differing product characteristics include dose (0.58 mg vs. 10 mg or 20 mg) and route of administration (injection into palpable Dupuytren's cord vs. oral), and frequency of administration (once every 3 to 4 weeks if needed vs. once daily). Xarelto is available in more than one strength and therefore this information will need to be provided on a prescription to dispense/administer the drug as intended.

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/s/

DENISE V BAUGH
05/12/2011

CAROL A HOLQUIST
05/12/2011



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 30, 2009

To: Rafel Dwaine Reeves, MD, Acting Director
Division of Medical Imaging and Hematology

Through: Kristina C. Arnwine, PharmD, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

From: Tselaine Jones Smith, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Proprietary Name, Label and Labeling Review

Drug Name(s): Xarelto (Rivaroxaban) Tablets 10 mg

Application Type/Number: IND 64,892
NDA 22-406

Applicant/Applicant: Bayer Healthcare Pharmaceuticals

OSE RCM #: 2007-1832
2009-637

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EXECUTIVE SUMMARY

This review is in response to a request from Bayer Healthcare Pharmaceuticals on August 21, 2007 for an assessment of the proposed proprietary name, Xarelto, regarding potential name confusion with other proprietary or established drug names in the usual practice settings.

DMEPA identified 15 names as having potential orthographic and/or phonetic similarity to Xarelto. Our Failure Mode Effects Analysis determined that the name similarity between Xarelto and the 15 names was unlikely to result in medication errors related to name confusion. Thus the Division of Medication Error Prevention and Analysis (DMEPA) has no objection to the proprietary name, Xarelto, for this product.

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.

The Label and Labeling Risk Assessment noted area of needed improvement; we provide recommendations in Section 5.2 that aim at reducing the risk of medication errors.

1 BACKGROUND

1.1 INTRODUCTION

This review is in response to a request from the Division of Medical Imaging and Hematology Products for assessment of the proprietary name, Xarelto, regarding confusion with other proprietary or established drug names. Additionally, container labels and carton and insert labeling were submitted for review and comment.

1.2 PRODUCT INFORMATION

Xarelto (Rivaroxaban Tablets) is a new molecular entity indicated for the prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing hip replacement or knee replacement surgery. The recommended oral dose is 10 mg taken once daily. The initial dose should be taken six to eight hours after surgery provided that hemostasis has been established. The treatment duration is two weeks (hip surgery) to five weeks (knee surgery). Xarelto can be taken with or without food. Xarelto will be available as 10 mg tablets.

2 METHODS AND MATERIALS

2.1 PROPRIETARY NAME RISK ASSESSMENT

This section consists of two sections which describe the methods and materials we use when conducting a proprietary name risk assessment (see Section 2.1) and label and labeling risk assessment (see Section 2.2). The primary focus for all of the assessments is to identify and remedy potential sources of medication error prior to drug approval. The Division of Medication Error Prevention and Analysis 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

FDA's Proprietary Name Risk Assessment considers the potential for confusion between the proposed proprietary name, Xarelto, 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 CDER.

For the proprietary name, Xarelto, DMEPA staff search a standard set of databases and information sources to identify names with orthographic and phonetic similarity (see section 2.1.1 for detail) and held a CDER Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name (see section 2.1.3).

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 2.4). 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. The Division of Medication Error Prevention and Analysis uses the clinical expertise of the DMEPA 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, DMEPA considers 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, we consider 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

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.

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.

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

For this review, particular consideration was given to drug names beginning with the letter ‘X’ 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 Xarelto, the DMEPA staff also consider the other orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (7 letters), upstrokes (three, capital letters ‘X’ and lower case letters ‘l’ and ‘t’), and cross-strokes (two, ‘t’ and capital letter x). Additionally, several letters in Xarelto may be vulnerable to ambiguity when scripted, including the letter ‘X’ may appear as the letters ‘T’, ‘K’, ‘F’, ‘V’ or ‘R’; the letter ‘a’ can appear as the lower case letters ‘o’, ‘e’ or ‘u’; lower case letter ‘r’ may look similar to lower case letters ‘s’, ‘v’ or ‘n’; lower case ‘l’ can appear as the letters ‘t’ or ‘f’; lower case letter ‘t’ appears as ‘l’, ‘b’, ‘f’ or ‘z’; and lower case ‘o’ can appear as the letters ‘e’, ‘u’ or ‘a’.

When searching to identify potential names that may sound similar to Xarelto, the DMEPA staff search for names with similar number of syllables (three), stresses (XA-rel-to, xa-REL-to or xa-rel-TO) and placement of vowel and consonant sounds. In addition, several letters in Xarelto may be subject to interpretation when spoken, including the letter ‘X’ may be interpreted as the letters ‘S’, ‘C’ or ‘Z’; the letter ‘a’ may be interpreted as the letters ‘o’, ‘e’, ‘u’ or ‘i’ and the letter ‘t’ may be interpreted as the letter ‘d’. 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 DMEPA staff also considers 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, the DMEPA staff were provided with the following information about the proposed product: the proposed proprietary name (Xarelto), the established name (Rivaroxaban), proposed indication of use (prophylaxis of venous thromboembolism in patients undergoing major orthopedic surgery such as hip replacement or knee replacement surgery), strength (10 mg), frequency of administration (once a day for two to five weeks), route of administration (oral) and dosage form of the product (tablet). Appendix A provides a more detailed listing of the product characteristics the DMEPA staff takes into consideration.

Lastly, the DMEPA staff also considers the potential for the proposed name to inadvertently function as a source of error for reasons other than name confusion. Postmarketing 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 we provide additional comments related to the safety of the proposed name or product based on their professional experience with medication errors.

2.1.2 Database and Information Sources

The proposed proprietary name, Xarelto, was provided to the Division of Medication Error Prevention and Analysis 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 Xarelto using the criteria outlined in 2.1.1. A standard description of the databases used in the searches is provided in Section 6. To complement the process, we 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

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. Artificial Intelligence in Medicine (2005)

some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, we 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.

2.1.3 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, Xarelto. Potential concerns regarding drug marketing and promotion related to the proposed names are also discussed. This group is composed of DMEPA staff and representatives from the Division of Drug Marketing, Advertising, and Communications (DDMAC) who have backgrounds in pharmacy and nursing.

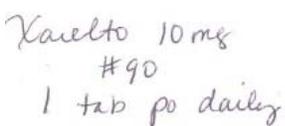
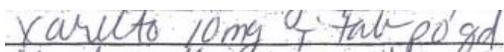
The pooled results of the DMEPA staff were presented to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend the addition of names, additional searches by the Safety Evaluator to supplement the pooled results, or general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

2.1.4 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 Xarelto 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 Xarelto in handwriting and verbal communication of the name, prescription orders are written, consisting of a combination of marketed and unapproved drug products, including the proposed name. These prescription orders are optically scanned and one prescription order 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 staff.

Figure 1. Xarelto Study (conducted on September 13, 2007)

HANDWRITTEN PRESCRIPTION AND MEDICATION ORDER	VERBAL PRESCRIPTION
<p><u>Outpatient</u></p> 	<p>Xarelto 10 mg # 90 One tablet by mouth daily</p>
<p><u>Inpatient</u></p> 	

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 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, we seek 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 than 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 Xarelto 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 Xarelto 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 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 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.

The Division of Medication Error Prevention and Analysis 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:

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

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 and another drug product.

In the event that we object 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 we will not object to the use of the proprietary name. If any of these conditions are met, then we will object to the use of the proprietary 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 1 through 5 are supported either by FDA Regulation or by external healthcare authorities, including the Institute of Medicine, World Health Organization, Joint Commission on the Accreditation of Healthcare Organizations, and Institute for Safe Medication Practices, who 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, we contend 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, postmarketing 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 Sponsor, 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 Sponsor'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, we believe 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 we object 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. We are likely to recommend that the Sponsor select an alternative proprietary name and submit the alternate name to the Agency for 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 Sponsor with recommendations that reduce or eliminate the potential for error would render the proposed name acceptable.

2.2 LABEL AND LABELING RISK ASSESSMENT

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container label and carton labeling communicate critical information including proprietary and established name, strength, form, container quantity, expiration date, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.⁷

For this product the Sponsor submitted on July 28, 2008, the following labels and insert labeling for our review (see Appendices F, G and H for images):

- Blister Label : 10 mg
- Container Label: 10 mg (30 count)
- Carton Labeling: 10 mg
- Package Insert Labeling (no image)

3 RESULTS

3.1 PROPRIETARY NAME RISK ASSESSMENT

3.1.1 Database and Information Sources

The searches yielded a total of 13 names as having some similarity to the name Xarelto.

Eleven (n=11) of the names were thought to look like Xarelto. These include Tarceva, Taxol, Kariva, Ranciclor, Paxil, Axert, Forteo, Xeroflo, Karela, Kaletra and Fareston. The remaining two names were thought to sound like Xarelto. These include Lorelco and Zarontin.

Additionally, DMEPA staff did not identify any United States Adopted Names (USAN) stems in the proposed proprietary name, as of April 27, 2009.

3.1.2 CDER 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.

⁷ Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

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 37 practitioners responded, and none of the responses overlapped with any existing or proposed drug names. Fourteen (n=14) of the participants interpreted the name correctly as “Xarelto”, with correct interpretation occurring in the inpatient written studies (n=7), the outpatient written studies (n=6) and the voice study (n=1). The remainder of the written and oral responses misinterpreted the drug name. In the verbal study, 13 of the 14 responses were misspelled phonetic variations of the proposed name, Xarelto. See Appendix B for the complete listing of interpretations from the verbal and written prescription studies.

3.1.4 Safety Evaluator Risk Assessment of Proposed Proprietary Name

Independent searches by the primary Safety Evaluator resulted in two additional names, Vasotec and Virilon, which were thought to look similar to Xarelto and represent a potential source of drug name confusion.

Fifteen (n=15) names were analyzed to determine if the drug names could be confused with Xarelto and if the drug name confusion would likely result in a medication error.

Seven (n=7) 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 potential name, could potentially be confused with any of the eight remaining names and lead to medication errors. This analysis determined that the name similarity between Xarelto and the identified names was unlikely to result in medication errors with any of the eight remaining products identified for the reasons presented in Appendices D through G.

3.2 LABEL AND LABELING RISK ASSESSMENT

Review of the container labels, carton and insert labeling indicate that the presentation of information on the proposed label and labeling introduces vulnerability to confusion that could lead to medication errors.

3.2.1 Presentation of Dosage Form on the Container Label

The dosage form is not presented immediately following the established name on the bulk container labels.

3.2.2 Size of Graphic on Principal Display Panel on the Carton Labels and Container Labeling

The size of the graphic is more prominent than the size of the proprietary name and established name.

3.2.3 Location of the (b) (4) Statement

The statement (b) (4) is presented on the principal display panel.

3.2.4 Blister Labeling and Package Insert Labeling

No comments at this time.

4 DISCUSSION

4.1 PROPRIETARY NAME RISK ASSESSMENT

Fifteen (n=15) names were evaluated for their potential similarity to the proposed name, Xarelto. The FMEA indicates that the proposed name is not likely to result in name confusion that could lead to medication errors.

4.2 LABEL AND LABELING RISK ASSESSMENT

Our evaluation of the labels and labeling noted several areas of needed improvement.

4.2.1 *Presentation of Dosage Form on the Container Label*

Our analysis noted that the only mention of the finished dosage form, 'tablets', appears with the net quantity statement. The usual presentation of information on label and labeling is: proprietary name, followed immediately by the established name which includes the dosage form and strength. Practitioners are accustomed to this layout and when such items appear in different locations, it takes longer to locate the information or information in its place can be confused.

4.2.2 *Size of Graphic on Principal Display Panel on the Carton Labels and Container Labeling*

As currently displayed, the size of the graphic on the principal display panel of the label and labeling is more prominent than the size of the established name and proprietary name. The proprietary name, established name and strength should be the most prominent information on the labels and labeling.

4.2.3 *Location of the statement*

(b) (4)

The statement (b) (4) on the principal display panel crowds the label and labeling and is duplicative. Relocating this statement to the side panel or deleting the statement will allow for more room on the principal display panel.

5 CONCLUSIONS AND RECOMMENDATIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Xarelto, is not vulnerable to name confusion that could lead to medication errors. Thus, the Division of Medication Error Prevention and Analysis (DMEPA) does not object to the proprietary name, Xarelto, for this product at this time. Additionally, DDMAC does not object to the proprietary name, Xarelto 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 approval of this application is delayed beyond 90 days from the signature date of this review, the proposed name must be resubmitted for evaluation.

The Label and Labeling Risk Assessment findings indicate that the presentation of information on the proposed label and labeling can be improved upon prior to approval and provides recommendations in Section 5.2.

5.1 COMMENTS TO THE DIVISION

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have any questions or need clarification, contact Janet Anderson, Project Manager, at 301-796-0675.

5.2 COMMENTS TO THE APPLICANT

5.2.1 *Proposed Proprietary Name*

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

If **any** of the proposed product characteristics are altered prior to approval of the marketing application or if the product approval is delayed beyond 90 days from the date of this review, the proposed name must be resubmitted for evaluation.

5.2.2 *Container Label and Carton Labeling*

Based upon our assessment of the labels and labeling, the Division of Medication Error Prevention and Analysis has identified the following areas of needed improvement.

1. Revise the established name on the bulk container label (30 tablets) to include the dosage form as follows: (b) (4)
2. The size of the graphic on the principal display panel is more prominent than the size of the established name and proprietary name. The proprietary name, established name and strength should be the most prominent information on the container label and carton labeling.
3. Delete or relocate to the side panel the (b) (4) statement as it crowds the principal display panel on the container label and carton labeling.

6 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. *AMF Decision Support System [DSS]*

DSS is a government database used to track individual submissions and assignments in 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:

The DMEPA staff considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. The Division of Medication Error Prevention 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. The 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* dissimilarly spelled drug name pairs to appear very similar to one another and the similar appearance of drug names when scripted has led to medication errors. The DMEPA staff applies 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, the DMEPA staff compares the pronunciation of the proposed proprietary name with the pronunciation of other drug names. If provided, we 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, we also consider 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	<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 Downstrokes Cross-strokes	<ul style="list-style-type: none"> Names may look similar when scripted, and lead to drug name confusion in written communication

		Dotted letters Ambiguity introduced 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	<ul style="list-style-type: none"> Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Appendix B: CDER Prescription Study Responses

Inpatient Medication Order	Outpatient Medication Order	Voice Prescription
Xaruto	Xaielto	Zorelto
Xarelto	Xarelto	Xeralto
Xarilto	Xarelto	Zerelto
Xarelto	Xaielto	Zerelto
Varilto	Xaielto	Zorelto
Xarelto	Xarelto	Zeralto
xarelto	Xarelto	Zerelto
Xarelto	Xaielto	Zerelto
Xarelto	Xarelto	Zerelto
Xaruto	Xaielto	Zarelto
Xaretto	Xarelto	Zerelto
Xarelto		Zorelto
		Zurelto
		Zirelto

Appendix C: Proprietary names that lack convincing orthographic and/or phonetic similarities to the proposed proprietary name Xarelto

Proprietary Name	Similarity to Xarelto
Tarceva	Look
Taxol	Look
Kariva	Look
Raniclor	Look
Paxil	Look
Axert	Look
Forteo	Look

Appendix D: Product that is discontinued and no generic equivalent is available

Proprietary Name	Similarity to Xarelto	Date
Lorelco Probuco Tablets 250 mg and 500 mg	Look and Sound	June 4, 2004

Appendix E: Products that have single strengths with multiple differentiating product characteristics.

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose (if applicable)	Product Characteristics
Xarelto (rivaroxaban tablets)		10 mg	10 mg (one tablet) orally once daily for two to five weeks	
Xeroflo Bismuth Tribromophenate Gauze Dressing	Look	3%	Place or pack dressing on or into wounds	Dosage Form (tablet vs. gauze dressing) Frequency of Administration (once daily vs. as directed by physician) Route of Administration (oral vs. topical)
Karela Bitter Melon capsules	Look	250 mg	1 to 2 capsules orally two times a day after meal	Frequency of Administration (once daily vs. twice daily) Prescription Status (prescription vs. over-the-counter)

Appendix F: Potential confusing name with numeric similarity or numerical overlap in strength and/or dose

Failure Mode: Name confusion	Causes (could be multiple)	Effects
Xarelto (rivaroxaban tablets)	Strength: 10 mg	Usual Dose: 10 mg orally once daily for two to five weeks
<p>Vasotec</p> <p>Enalapril Maleate</p> <p><u>Dosage Form and Strengths:</u></p> <p>Tablet: 2.5 mg, 5 mg, 10 mg and 20 mg</p> <p>Solution for Injection: 1.25 mg/mL</p> <p><u>Usual Dose:</u></p> <p>10 mg (one tablet) to 40 mg orally daily divided in one to two doses</p> <p>1.25 mg/dose given intravenously over 5 minutes every 6 hours</p>	<p><u>Orthographic similarities</u></p> <p>Both names contain seven letters</p> <p>The beginnings of the two names may appear similar when scripted ('Xare-' vs. 'Vaso-')</p> <p><u>Overlapping product characteristics</u></p> <p>Strength (10 mg)</p> <p>Dose (10 mg)</p> <p>Dosage form (tablet)</p> <p>Frequency of administration (once daily)</p> <p>Route of administration (oral)</p>	<p>Orthographic differences in the names minimize the likelihood of medication error between the two products in the usual practice setting.</p> <p><i>Rationale:</i></p> <p>The risk for medication error is minimized by the orthographic differences in the endings of the two names ('-lto' vs. '-tec') which look different when scripted.</p> <div style="text-align: center;"> <p>Xarelto</p> <p>Vasotec</p> </div>
<p>Virilon</p> <p>Methyltestosterone Capsule</p> <p>Testosterone Cypionate in Oil for Injection</p> <p><u>Dosage form and strength:</u></p> <p>Capsule: 10 mg</p> <p>Oil for Injection: 200 mg/mL</p> <p><u>Usual dose:</u></p> <p>Capsule: 5 mg to 50 mg orally one to four times a day depending on indication</p> <p>Injection: 50 mg to 400 mg given intramuscularly once every 2 to 4 weeks</p>	<p><u>Orthographic similarities</u></p> <p>Both names contain seven letters</p> <p>The middle letters of the two names may appear similar when scripted ('Xarel-' vs. 'Viril-')</p> <p><u>Overlapping product characteristics</u></p> <p>Strength (10 mg)</p> <p>Dose (10 mg)</p> <p>Dosage form (tablet/capsule)</p> <p>Frequency of administration (once daily)</p> <p>Route of administration (oral)</p>	<p>Orthographic differences in the names minimize the likelihood of medication error between the two products in the usual practice setting.</p> <p><i>Rationale:</i></p> <p>The endings ('-to' vs. '-on') of the two names look different when scripted.</p> <div style="text-align: center;"> <p>Xarelto</p> <p>Virilon</p> </div>

Failure Mode: Name confusion	Causes (could be multiple)	Effects
Xarelto (rivaroxaban tablets)	Strength: 10 mg	Usual Dose: 10 mg orally once daily for two to five weeks
Zarontin Ethosuxamide <u>Dosage form and strength:</u> Capsule: 250 mg Syrup: 250 mg/5 mL <u>Usual Dose:</u> 250 mg (1 tablet or 1 teaspoon) orally twice daily	<u>Orthographic similarities</u> Both names are similar lengths (seven letters vs. eight letters) The first four letters of the two names may appear similar when scripted ('Xare-' vs. 'Zaro-') <u>Phonetic similarities</u> Both names contain three syllables The first two syllables of both names ('Xa-rel-' vs. 'Za-ron-') sound similar when spoken <u>Overlapping product characteristics</u> Dose (1 tablet)	Orthographic and phonetic differences and the frequency of administration minimize the likelihood of medication error in the usual practice setting. <i>Rationale:</i> The length of the name Zarontin is longer than the name Xarelto when scripted. Additionally, the endings ('-lto' vs. '-ntin') of the two names look different when scripted <div style="text-align: center;"> Xarelto Zarontin </div> The 'l' sound at the end of the second syllable of Xarelto sounds different from the 'n' sound of the second syllable of Zarontin. In addition the long 'o' sound at the Xarelto sounds different than the 'in' sound at the end of Zarontin. Xarelto is dosed once daily versus Zarontin is dosed twice daily.
Fareston Toremifene <u>Dosage form and strength:</u> 60 mg capsules <u>Usual dose:</u> 60 mg (1 tablet) orally once daily until disease progression	<u>Orthographic similarities</u> Both names are similar lengths (seven letters vs. eight letters) The first four letters of the two names may appear similar when scripted ('Xare-' vs. 'Fare-') <u>Overlapping product characteristics:</u> Dose (1 tablet) Frequency of administration (once daily)	Orthographic differences minimize the likelihood of medication error in the usual practice setting. <i>Rationale:</i> The endings of the two names ('-lto' vs. '-ston') differentiate the two names when scripted. <div style="text-align: center;"> Xarelto Fareston </div>

Failure Mode: Name confusion	Causes (could be multiple)	Effects
Xarelto (rivaroxaban tablets)	Strength: 10 mg	Usual Dose: 10 mg orally once daily for two to five weeks
<p>Kaletra</p> <p>Lopinavir/Ritonavir</p> <p><u>Dosage form and strength:</u></p> <p>Tablets:</p> <p>100 mg/25 mg (pediatrics)</p> <p>200 mg/50 mg</p> <p>Solution:</p> <p>80 mg/20 mg/mL</p> <p><u>Usual dose:</u></p> <p><i>Tablets:</i></p> <p>400 mg/100 mg (given as two 200 mg/50 mg tablets) orally twice daily with or without food</p> <p>800 mg/200 mg (given as four 200 mg/50 mg tablets) orally once daily taken with or without food.</p> <p><i>Oral Solution:</i></p> <p>400 mg/100 mg (5 mL) orally twice daily with food</p> <p>800 mg/200 mg (10 mL) orally once daily with food.</p> <p>Taken in combination with other antiretroviral agents</p>	<p><u>Orthographic similarities</u></p> <p>Both names have similar beginnings ('Xa-' vs. 'Ka-') and endings ('-to' vs. '-tra')</p> <p><u>Overlapping product characteristics:</u></p> <p>Strength (10 mg vs. 100 mg/25 mg for pediatrics)</p> <p>Frequency of Administration (once daily)</p> <p>Dosage form (tablets)</p>	<p>Orthographic and product characteristic differences minimize the likelihood of medication error in the usual practice setting.</p> <p><i>Rationale:</i></p> <p>The middle letters ('-rel-' vs. '-le-') differentiate the two names when scripted.</p> <p>The positions of the upstrokes will differentiate the names when scripted. Xarelto has two upstrokes ('-lt-') at the end of the name in the fifth and sixth positions and Kaletra has an upstroke ('l') in the middle of the name in the third position and one ('t') located in the fifth position of the name.</p> <div style="text-align: center;"> <p>Xarelto</p> <p>Kaletra</p> </div> <p>Kaletra requires concomitant therapy with fosamprenavir, efavirenz, nelfinavir or nevirapine</p> <p><i>vs. Kaletra Tablets</i></p> <p>The products differ in their doses (10 mg given as 1 tablet vs. 400 mg/100 mg, given as two 200 mg/50 mg tablets or 800 mg/200 mg given as four 200 mg/50 mg tablets)</p>

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