CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-926

PROPRIETARY NAME REVIEW(S)

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

Date:	April 14, 2008
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Thru:	Linda Y. Kim-Jung, PharmD, Team Leader Denise P. Toyer, PharmD, Deputy Director Carol A. Holquist, R.Ph., Director Division of Medication Error Prevention, HFD-420
From:	Loretta Holmes, BSN, PharmD, Safety Evaluator Division of Medication Error Prevention, HFD-420
Subject:	Proprietary Name, Label, and Labeling Review
Drug Name:	Treximet (Sumatriptan and Naproxen Sodium) Tablets 85 mg/500 mg
Application Type/Number:	NDA 21-926
Applicant:	Pozen, Inc.
OSE RCM #:	2008-433

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

Contents

EXECUTIVE SUMMARY 3
1 BACKGROUND 3
1.1 Introduction 3
1.2 Regulatory History 3
1.3 Product Information 3
2 METHODS AND MATERIALS 3
2.1 Proprietary Name Risk Assessment 4
2.2 Label and Labeling Risk Assessment 8
3 RESULTS 9
3.1 Proprietary Name Risk Assessment 9
3.2 Label and Labeling Risk Assessment 10
4 DISCUSSION 11
4.1 Proprietary Name Risk Assessment 11
4.2 Label and Labeling Risk Assessment 11
5 CONCLUSIONS 12
6 RECOMMENDATIONS 13
6.1 Comments to the Division 13
6.2 Comments to the Applicant 13
7 REFERENCES 14
APPENDICES 16

EXECUTIVE SUMMARY

The results of the Proprietary Name Risk Assessment found that the proposed name,Treximet, has some similarity to other proprietary and established drug names, but the findings of the FMEA indicate that the proposed name does not appear to be vulnerable to name confusion that could lead to medication errors. Thus, the Division of Medication Error Prevention has no objections to the use of the proprietary name, Treximet, for this product.

The results of the Label and Labeling Risk Assessment found that the presentation of the statement of strength on the container labels and carton labeling and omission of the drug administration precaution on the carton labeling render the labels and labeling vulnerable to confusion that could lead to medication errors. The Division of Medication Error Prevention and Analysis believes the risks we have identified can be addressed and mitigated prior to drug approval and provide recommendations in Section 6.

However; if any of the proposed product characteristics as stated in this review are altered prior to approval of the product, the Division of Medication Error Prevention rescinds this Risk Assessment finding, and recommends that the name be resubmitted for review. Additionally, if product approval is delayed beyond 90 days from the signature date of this review, the proposed name must be resubmitted for re-evaluation.

1 BACKGROUND

1.1 INTRODUCTION

This review was written in response to a request from the Division of Neurology Products (HFD-120) for re-assessment of the proposed proprietary name, Treximet, regarding potential name confusion with other proprietary or established drug names.

1.2 REGULATORY HISTORY

The Division of Medication Error Prevention previously reviewed the names [redacted] (primary) and Treximet (secondary) for this NDA (see OSE Review 2007-1571, dated August 16, 2007) and had no objections to the use of those names at that time. The Applicant has chosen the secondary name, Treximet, for their product.

1.3 PRODUCT INFORMATION

Treximet contains sumatriptan (as the succinate), a selective 5-hydroxytryptamine$_1$ (5-HT$_1$) receptor subtype agonist, and naproxen sodium, a member of the arylacetic acid group of nonsteroidal anti-inflammatory drugs. Treximet is indicated for the acute treatment of migraine attacks with or without aura in adults. Treximet will be available as 85 mg/500 mg tablets. The recommended dose is one tablet with a maximum dose of two tablets in 24 hours. Dosing of tablets should be at least two hours apart. Treximet may be administered with or without food. Tablets should not be split, crushed, or chewed. Treximet has a boxed warning in the package insert labeling concerning cardiovascular and gastrointestinal risks. The product will be supplied in compact containers of 9 tablets with a specially formulated, non-removable dessicant.

2 METHODS AND MATERIALS

This section consists of two sections which describe the methods and materials used by the Division of Medication Error Prevention Medication Error Staff conducting a proprietary name risk assessment (see 2.1 Proprietary Name Risk Assessment). The primary focus for both of the assessments is to identify and remedy potential sources of medication error prior to drug approval. The Division of Medication Error Prevention defines a medication error as any preventable event that may cause or lead to inappropriate

medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [1]

2.1 PROPRIETARY NAME RISK ASSESSMENT

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

For the proprietary name,Treximet, the Medication Error Staff of the Division of Medication Error Prevention search a standard set of databases and information sources to identify names with orthographic and phonetic similarity (see Sections 2.1.1 for detail) and held a CDER Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name (see 2.1.1.2). The Division of Medication Error Prevention normally conducts internal CDER prescription analysis studies and, when provided, external prescription analysis studies results are considered and incorporated into the overall risk assessment. However, since this name was previously evaluated, CDER prescription analysis studies were not conducted upon re-review of Treximet.

The Safety Evaluator assigned to the Proprietary Name Risk Assessment is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name (see detail 2.1.3). The overall risk assessment is based on the findings of a Failure Modes 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 uses the clinical expertise of the Medication Error Staff to anticipate the conditions of the clinical setting that the product is likely to be used in based on the characteristics of the proposed product.

In addition, the product characteristics provide the context for the verbal and written communication of the drug names and can interact with the orthographic and phonetic attributes of the names to increase the risk of confusion when there is overlap, or, in some instances, decrease the risk of confusion by helping to differentiate the products through dissimilarity. As such, the Staff 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, the Division of Medication Error Prevention considers the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.[3]

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

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

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

2.1.1 Search Criteria

The Medication Error Staff consider the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted as outlined in Appendix A.

For this review, particular consideration was given to drug names beginning with the letter 'T' 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.[45]

To identify drug names that may look similar to Treximet, the staff also consider the orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (8 letters), upstrokes (2, capital letter 'T' and lowercase 't'), downstrokes (none), cross-strokes (2, lowercase 'x' and 't'), and dotted letters ('i'). Additionally, several letters in Treximet may be vulnerable to ambiguity when scripted, including the letter 'T' which may appear as uppercase 'F', 'L', and 'Z'; lower case 'r' appear as a lower case 'n' or 's'; lowercase 'e' appear as lowercase undotted 'i' or 'l'; lowercase 'x' appear as a lowercase 'f', 'k', 'n', 'p', 'r' or 't'; lowercase 'i' appear as lowercase 'e' or 'l'; lowercase 'm' appear as lowercase 'n', 'ss', or 'z'; and lowercase 't' appear as lowercase 'f', 'k', or 'x'. As such, the Staff also consider these alternate appearances when identifying drug names that may look similar to Treximet.

When searching to identify potential names that may sound similar to Treximet, the Medication Error Staff search for names with similar number of syllables (three), stresses (TREX-i-met, trex-I-met, or trex-i-MET), and placement of vowel and consonant sounds. Additionally, "Trex" can sound like "Trac" when pronounced. The Sponsor's intended pronunciation of the proprietary name could not be expressly taken into consideration, as this was not provided with the proposed name submission.

The Staff also 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 Medication Error Staff were provided with the following information about the proposed product: the proposed proprietary name (Treximet), the established name (sumatriptan and naproxen sodium), proposed indication of use (acute treatment of migraine attack), strength (85 mg/500 mg), dose (one tablet), frequency of administration (up to two tablets in a 24 hour period with a minimum of 2 hours between doses), route (oral) and dosage form of the product (tablet). Appendix A provides a more detailed listing of the product characteristics the Medication Error Staff general take into consideration.

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

2.1.1.1 Databases and information sources

The proposed proprietary name, Treximet, was provided to the Medication Error Staff 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 Treximet using the criteria

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

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

outlined in 2.1.1. A standard description of the databases used in the searches is provided in Section 7. To complement the process, the Medication Error 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 Medication Error Staff review the USAN stem list to determine if any USAN stems are present within the proprietary name. The findings of the individual Safety Evaluators were then pooled and presented to the Expert Panel.

2.1.1.2 CDER Expert Panel Discussion

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

The pooled results of the Medication Error 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.

2.1.2 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 Modes 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 a 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 Treximet 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 Tresimet 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.

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

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

1. DDMAC finds the proposed proprietary name misleading from a promotional perspective, and the review Division concurs with DDMAC's findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a trade name or otherwise. [21 U.S.C 321(n); see also 21 U.S.C. 352(a) & (n)].
2. The Division of Medication Error Prevention 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. Medication Error Staff identify a potential source of medication error within the proposed proprietary name. The proprietary name may be misleading, or inadvertently introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug another drug product.

In the event that the Division of Medication Error Prevention 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/Applicant; however, the safety concerns set forth in criteria 1 through 5 are supported either by FDA Regulation or by external healthcare authorities, including the Institute of Medicine, World Health Organization, Joint Commission, and Institute for Safe Medication Practices, 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, the Division of Medication Error Prevention contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a

predictable and preventable source of medication error that, in many instances, can be identified and remedied prior to approval to avoid patient harm.

Additionally, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to remedy post-approval. Educational efforts and so on are low-leverage strategies that have proven to have limited effectiveness at alleviating the medication errors involving drug name confusion. Higher-leverage strategies, such as drug name changes, have been undertaken in the past; but at great financial cost to the 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 (e.g. new form introduced like Lamisil) (see limitations of the process in Section 4).

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

2.2 LABEL AND LABELING RISK ASSESSMENT

This section describes the methods and materials used by the Division of Medication Error Prevention Medication Error Staff to conduct a label, labeling, and/or packaging risk assessment (see Section 3, Results). The primary focus of the assessments is to identify and remedy potential sources of medication errors prior to drug approval. The Division of Medication Error Prevention defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [7]

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, 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 United States Pharmacopeia-Institute for Safe Medication Practices Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.[8]

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

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

Because the Division of Medication Error Prevention staff analyzes reported misuse of drugs, the Division of Medication Error Prevention staff is able to use this experience to identify potential errors with all medications similarly packaged, labeled or prescribed. The Division of Medication Error Prevention uses FMEA and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provide recommendations that aim at reducing the risk of medication errors.

The Division of Medication Error Prevention reviewed the following labels and labeling submitted by the Applicant on January 15, 2008. See Appendix B for pictures of the labels and labeling.

- Container Labels: Top, bottom, and sides
- Carton Labeling: Inside and outside
- Package Insert Labeling (no image)
- Medication Guide (no image)
- Compact container (photo only)
- Business Reply Cards: Request for Information and Savings

3 RESULTS

3.1 PROPRIETARY NAME RISK ASSESSMENT

3.1.1 Database and information sources

The Division of Medication Error Prevention conducted a search of the internet, several standard published databases and information sources (see Section 7 References) for existing drug names which sound-alike or look-alike to Treximet to a degree where potential confusion between drug names could occur and result in medication errors in the usual clinical practice settings. In total, thirty-nine names were identified as having some similarity to the name Treximet: Avandamet, Anzemet, Fortamet, Janumet, Trexonil, Trisenox, [redacted], Trexim, Tagamet, Cesamet, Tetramed, Timenton, Trexinest, Sinemet, [redacted] Feridex, Tofranil, Tiamate, Triatex, Tretin-X, Roxicet, Texacort, Frexivit H/C, Fexmid, Fioricet, Flexeril, Fiorinal, [redacted], Trimetrexate, Tritec, Trest, Trexamette, Trexima*** (a previously proposed name for this product), Trexina, Tetrex, Triacet, Trexall, Trexan, and Trexamate.

Fourteen names were previously evaluated in OSE Review 2007-1571, dated August 16, 2007. The twenty-five names not previously reviewed are: Avandamet, Anzemet, Trexonil, [redacted] Trexim, Tetramed, Timentin, Trexinest, Sinemet, [redacted], Feridex, Tofranil, Tiamate, Tretin-X, Texacort, Frexivit H/C, Fexmid, Fiorinal, [redacted], Tritec, Trest, Trexamette, Trexina, Tetrex, and Trexamate.

Nineteen of the twenty-five names were thought to look like Treximet, which include: Avandamet, Anzemet, Trexonil, [redacted] Trexim, Tetramed, Timentin, Trexinest, Sinemet, [redacted] Feridex, Tofranil, Tiamate, Tretin-X, Texacort, Frexivit H/C, Fexmid, Fiorinal, and [redacted]. Two names, Tritec and Trest, were thought to sound like Treximet. Four names, Trexamette, Trexina, Tetrex, and Trexamate, were thought to look and sound similar to Treximet.

Additionally, the Division of Medication Error Prevention did not identify any USAN stems in the name Treximet.

3.1.2 Expert panel discussion

The Expert Panel reviewed the pool of names identified by the Division of Medication Error Prevention staff (see section 3.1.1. above), and did not note any additional names thought to have orthographic or phonetic similarity to Treximet and have the potential for confusion.

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 Safety Evaluator Risk Assessment of Proposed Proprietary Name

Independent searches by the primary Safety Evaluator did not identify any additional names, thought to look similar to Treximet and represent a potential source of drug name confusion. However, the primary Safety Evaluator determined that one of the previously reviewed names in OSE review 2007-1571, Fortamet, needed to be reassessed due to look-alike similarity with Treximet. As such, a total of 26 names were analyzed to determine if the drug names could be confused with Treximet, and if the drug name confusion would likely result in a medication error.

All of the identified names were determined to have some orthographic and/or phonetic similarity to Treximet, and thus determined to present some risk for confusion. Failure modes and effects analysis was then applied to determine if the proposed name, Treximet, could potentially be confused with any of the 26 names and lead to medication error.

The FMEA determined that the name similarity between Treximet and the identified names was unlikely to result in medication errors for all 26 products. Six of the names identified: Tetrex, Timentin, Feridex, Fexmid, Tritec, and Trest were not considered further because they lack convincing orthographic and/or phonetic similarities with Treximet (see Appendix C).

One name, [redacted] was a previously proposed names for this product and determined unacceptable by the Division of Medication Error Prevention. Three names, Frexivite H/C (Mexico), Trexamette (Japan), and Trexina (Argentina) are for foreign products for which product characteristic information could not be found (see Appendix D). One name, Trexim, is a foreign trademark (Poland and Sweden), however, we were unable to determine that it is the name of a drug product (see Appendix D). Tiamate, is the name of an FDA approved product that was never marketed in the United States and [redacted] is the name of a product deemed not approvable by the Agency in 2000. [redacted] is a pending name within the Agency, however, the product strengths and dose do not overlap with Treximet. Trexonil is an injectable veterinary drug product and thus, has a different context of use. The following two products have been discontinued: Trexinest and Tetramed (see Appendix E). Trexinest (unable to find product characteristic information) was discontinued in 1976 and Tetramed (a branded generic) in 1997. Trexamate is a trademark that expired in November 1992[9] (we were unable to identify the actual product or service) and thus poses minimal risk for error in the usual practice setting.

Three names, Sinemet, Tretin-X, and Texacort were determined to have some orthographic and/or phonetic similarity to Treximet, and thus, determined to present some risk of confusion. For these names, FMEA determined that medication errors were unlikely because the products do not overlap in strength or dosage with Treximet (see Appendix F). Four names: Fortamet, Avandamet, Anzemet, Tofranil, and Fiorinal have strengths that contain numbers with some numerical overlap with the strength of one of the ingredients in Treximet but analysis of the failure mode did not determine the effect of this similarity to result in medication errors in the usual practice setting (see Appendix G).

3.2 LABEL AND LABELING RISK ASSESSMENT

3.2.1 General Comments

The dosage form statement is next to the statement of strength.

The statement of strength is not prominent on the labels and labeling.

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[9] http://www.uspto.gov, accessed March 23, 2008.

The "New" callout is unnecessary and distracting.

3.2.2 Container Labels

3.2.2.1 Sides, Top, and Bottom

See General Comments, 3.2.1.

3.2.3 Carton Labeling

3.2.3.1 Outside

[redacted]

3.2.3.2 Inside

The Division of Medication Error Prevention has no comments.

3.2.4 Package Insert Labeling

The Division of Medication Error Prevention has no comments.

3.2.5 Medication Guide

The Division of Medication Error Prevention has no comments.

3.2.6 Business Reply Cards

The business reply cards are promotional materials that should be consulted to the Division of Drug Advertising, Marketing, and Communications.

4 DISCUSSION

4.1 PROPRIETARY NAME RISK ASSESSMENT

The results of the Proprietary Name Risk Assessment found that the proposed name, Treximet, has some similarity to other proprietary and established drug names, but the findings of the FMEA indicate that the proposed name does not appear to be vulnerable to name confusion that could lead to medication errors. Thus, we have no objection to the use of the name, Treximet, for this product.

4.2 LABEL AND LABELING RISK ASSESSMENT

Our Label and Labeling Risk Assessment found that the presentation of the statement of strength and the omission of the drug administration precaution statement render the container labels and/or carton labeling vulnerable to confusion that could lead to medication errors. Specifically, we noted that the

[redacted]

[redacted]

[redacted] We realize that the container labels may be too small to add this warning but the carton labeling has room to include it. Although the container label is small, this is an important warning that should be considered for addition to both the container label and carton labeling. The size of the container label can be increased. Additionally, this information could be placed on the container label if the [redacted] wording is deleted. This warning is more important than the web site information. Thus, the user should know this warning in order to ensure that the drug is administered properly.

[redacted]

We noted that the Applicant submitted business cards for review and comment. However, this material is promotional in nature and, thus, not subject to evaluation by the Division of Medication Error Prevention. The Division of Drug Marketing, Advertising, and Communications is the appropriate Division to have review this material.

5 CONCLUSIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Treximet, does not appear to be vulnerable to name confusion that could lead to medication errors. Thus, the Division of Medication Error Prevention has no objection to the use of the name, Treximet, for this product. Additionally, DDMAC does not object to the proposed name, Treximet, from a promotional perspective.

Our Label and Labeling Risk Assessment found that the presentation of the statement of strength and the omission of the precautionary statement [redacted] render the container labels and/or carton labeling vulnerable to confusion that could lead to medication errors. As currently presented, the labels and labeling can be improved so as to provide safer container labels and carton labeling that may help to prevent unnecessary medication errors with the use of the product.

If **any** of the proposed product characteristics as stated in this review are altered prior to approval of the product; the Division of Medication Error Prevention rescinds this Risk Assessment finding, and recommends that the name, labels, and labeling be resubmitted for review. If 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. Additionally, if the product approval is delayed beyond 90 days from the date of this review, the proposed name must be resubmitted for evaluation.

Overall, our Risk Assessment is limited by our current understanding of medication errors and causality. The successful application of Failure Modes and Effect Analysis depends upon the learning gained for a spontaneous reporting program. It is quite possible that our understanding of medication error causality would benefit from unreported medication errors; and, that this understanding could have enabled the Staff to identify vulnerability in the proposed name, packaging, and labeling that was not identified in this assessment. To help minimize this limitation in future assessments, we encourage the Applicant to provide the Agency with medication error reports involving their marketed drug products regardless of adverse event severity.

6 RECOMMENDATIONS

We recommend the revisions below be implemented in the interest of minimizing user errors and maximizing patient safety. The Division of Medication Error Prevention would appreciate feedback on the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention on any correspondence to the sponsor pertaining to this issue. If you have further questions or need clarifications, please contact Daniel Brounstein, OSE Project Manager, at 301-796-0674.

6.1 COMMENTS TO THE DIVISION

6.1.1 The Division of Medication Error Prevention does not object to the use of the proprietary name, Treximet, for this product. If any of the proposed product characteristics as stated in this review are altered prior to approval of the product, the Division of Medication Error Prevention rescinds this Risk Assessment finding, and recommends that the name, labels, and labeling be resubmitted for review.

6.1.2 If the product approval is delayed beyond 90 day from the signature date of this review, the proposed name and its labels and labeling must be resubmitted for evaluation.

6.1.3 The business reply cards are promotional in nature and, thus, we recommend the Division consult the Division of Drug Marketing, Advertising, and Communications regarding this promotional material.

6.2 COMMENTS TO THE APPLICANT

6.2.1 General Comments

6.2.1.1 Relocate the dosage form statement so that it is to the right of and adjacent to the established name or, alternatively, relocate the statement of strength so that is is below the dosage form statement (see examples below).

Treximet (sumitriptan and naproxen sodium) Tablets 85 mg/500 mg

6.2.1.2 Additionally, increase the size and prominence of the statement of strength.

6.2.1.3 Remove the "New" callout from the labels and labeling.

6.2.2 Container Labels

6.2.2.1 Sides, Top, and Bottom

See General Comments, 6.2.1.

Delete the wording [redacted]

Add the drug administration precautionary statement [redacted] or similar verbiage.

6.2.3 Carton Labeling

6.2.3.1 Outside

Add the drug administration precautionary statement [redacted] or similar verbiage.

Add the wording [redacted] or similar verbiage.

6.2.4 Medication Guide

The Division of Medication Error Prevention has no comments.

7 REFERENCES

1. Adverse Events Reporting System (AERS)

AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufactures that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential postmarketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

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

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

3. Phonetic and Orthographic Computer Analysis (POCA)

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

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

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

5. AMF Decision Support System [DSS]

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

6. Division of Medication Errors and Technical Support proprietary name consultation requests

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

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

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

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

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

9. *WWW location http://www.uspto.gov.*

Provides information regarding patent and trademarks.

10. *Clinical Pharmacology Online (http://weblern/)*

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

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

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

12. *Natural Medicines Comprehensive Databases (http://weblern/)*

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

13. *Stat!Ref (http://weblern/)*

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

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

List contains all the recognized USAN stems.

15. *Red Book Pharmacy's Fundamental Reference*

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

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

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

17. Medical Abbreviations Book

Contains commonly used medical abbreviations and their definitions.

Use standard format for citations for previous OSE reviews; literature.

APPENDICES

Appendix A:

The Medication Error Staff consider 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 compare the spelling of the proposed proprietary name with the proprietary and established name of existing and proposed drug products because similarly spelled names may have greater likelihood to sound similar to one another when spoken or look similar to one another when scripted. The Medication Error Staff also examine the orthographic appearance of the proposed name using a number of different handwriting samples. Handwritten communication of drug names has a long-standing association with drug name confusion. Handwriting can cause similarly *and* dissimilarly spelled drug name pairs to appear very similar to one another and the similar appearance of drug names when scripted has lead to medication errors. The Medication Error Staff apply their expertise gained from root-cause analysis of such medication errors to identify sources of ambiguity within the name that could be introduced when scripting (e.g. "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 Medication Error Staff compare the pronunciation of the proposed proprietary name with the pronunciation of other drug names. If provided, the Division of Medication Error Prevention will consider the Sponsor's intended pronunciation of the proprietary name. However, because the Sponsor 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	• 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-stokes Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	• Names may look similar when scripted, and lead to drug name confusion in written communication
Sound-alike	Phonetic similarity	Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics	• Names may sound similar when pronounced and lead to drug name confusion in verbal communication

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_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Proprietary Name Review 11

Appendix C:

Names that lack convincing orthographic and/or phonetic similarities

Name	Similarity to Treximet
Tetrex	Look
Timentin	Look
Feridex	Look
Fexmid	Look
Tritec	Sound
Trest	Sound

Appendix D:

Foreign Names

Name	Similarity to Treximet	Country
Frexivite H/C	Look	Mexico
Trexamette	Look and Sound	Japan
Trexina	Look and Sound	Argentina
Trexim	Look	Poland and Sweden

Appendix E:

Discontinued Products

Name	Similarity to Treximet
Trexinest	Look
Tetramed	Look

Appendix F: Products with no numerical overlap in strength or dose.

Product name with potential for confusion	Similarity to Treximet	Strength	Usual Dose (if applicable)
Treximet (Sumatriptan and Naproxen Sodium)		**85 mg/500 mg**	**Usual dose: One tablet. Maximum of 2 tablets in 24 hours. Dosing of tablets should be at least 2 hours apart.**
Sinemet	Look	10/100, 25/100, 25/250 tablets	25/100 or 10/100 three or four times per day, may be increased until a dose of 8 tablets per day is reached
Tretin-X	Look	0.01%, 0.025%, and 0.05% topical cream; 0.01% and 0.025% topical gel	Apply once daily in the evening or before bedtime
Texacort	Look	1% and 2.5% topical solution	Apply two to four times per day

Appendix G: Potentially confusing names with numerical overlap in strength or dose

Treximet (Sumatriptan and Naproxen Sodium)	**85 mg/500 mg**	**Usual dose: One tablet. Maximum of 2 tablets in 24 hours. Dosing of tablets should be at least 2 hours apart.**
Failure Mode: Name confusion	**Causes (could be multiple)**	**Analysis**
Fortamet	Orthographic similarity ("F" vs. "T" and "tamet" vs. "ximet") Potential numerical overlap in strength. ("500 mg" in Fortamet vs. "500 mg" in Treximet 85 mg/500 mg).	Medication errors unlikely to occur because Fortamet is available in two strengths (500 mg and 1,000 mg). *Rationale:* The potential for overlap exists if the strength for Treximet is written as 500 mg. However, this is unlikely to occur since Treximet is a combination product with only one strength available. It is more likely that the entire strength will be written or that the strength will not be written and the dose specified at "1 tablet".

Avandamet	Orthographic similarity ("-imet" vs. "amet") Potential numerical overlap in strength. ("500 mg" in Avandamet 2 mg/500 mg and 4 mg/500 mg vs. "500 mg" in Treximet 85 mg/500 mg). Note: Avandamet is available in the following strengths: 2 mg/500 mg, 2mg/1000 mg 4 mg/500 mg 4 mg/1000 mg	Medication errors are unlikely to occur due to orthographic differences in the names in addition to the "500 mg" portion being the same in the 2 mg/500 mg and 4 mg/500 mg strengths of Avandamet. *Rationale:* The risk for medication error is minimized by orthographic differences in the names. The beginning letters of the names look different ("Avand-" vs. "Trex-"). Additionally, the upstroke in the letter "d" in Avandamet helps to differentiate the names. Furthermore, the number of letters in the names differ (nine vs. eight) which makes Avandamet appear slightly longer in length. The potential for overlap exists if the strength for Avandamet or Treximet is written as 500 mg. However, this is unlikey to occur with either product. Avandamet is available in 2 mg/500 mg and 4 mg/500 mg strengths so the milligram amount for both ingredients would have to be written on a prescription for clarity (the other strengths available are 2 mg/1000 mg and 4 mg/1000 mg and so the same rationale would apply). Additionally, the Treximet strength or dose is unlikely to be written as 500 mg because the product is available in only one strength in addition to the fact that it contains two ingredients.
Anzemet	Orthographic similarity ("-imet" vs. "–emet") Potential numerical overlap in strength. (50 mg Anzemet vs. 500 mg in Treximet 85 mg/500 mg). Overlap could be exacerbated if a trailing zero (e.g. 50.0) is included with Anzemet 50 mg.	Medication error unlikely to occur due to orthographic differences in the names. *Rationale*: The risk for medication errors is minimized by orthographic differences in the names. The beginning letters of the names look different ("Anze-" vs. "Trex-"). Additionally, the letter "z" can be scripted with a downstroke. Furthermore Treximet contains more letters (eight vs. seven) which makes the name appear slightly longer in length. These factors help to differentiate the names. The potential for overlap exists if the strength or dose of Treximet is written as "500 mg" and that of Anzemet is written as "50.0 mg". However, Treximet is unlikely to be ordered in this manner because the product is available in only one strength in addition to the fact that it contains two ingredients. A more likely scenario would be for the Treximet strength to be omitted and the dose written as "1 tablet" whereas the Anzemet strength or dose would be specified because multiple strengths are available. Furthermore, usual practice would not typically involve the inclusion of trailing zeros, though medication errors have been linked to this dangerous habit. Numerous campaigns (Joint Commission, Institute for Safe Medication Practices,

		and the Food and Drug Administration) to eliminate use of trailing zeros when communicating drug information should help to further reduce risk of medication error.
Tofranil	Orthographic similarity ("T") and ("-imet" vs. "-anil") Numerical overlap in strengths (50 mg Tofranil vs. 500 mg in Treximet). Overlap could be exacerbated if a trailing zero (e.g. 50.0) is included with Tofranil 50 mg	Orthographic differences in the names minimize the likelihood of medication error in the usual practice setting. *Rationale:* The risk for medication error is minimized by the orthographic differences in the names. The beginning letters of the names look different ("Tof-" vs. "Trex-"). Additionally, the letter "f" has an upstroke and downstroke which helps to differentiate the names. The potential for overlap exists if the strength or dose of Treximet is written as "500 mg" and that of Tofranil is written as "50.0 mg". However, Treximet is unlikely to be ordered in this manner because the product is available in only one strength in addition to the fact that it contains two ingredients. Furthermore, usual practice would not typically involve the inclusion of trailing zeros, though medication errors have been linked to this dangerous habit. Numerous campaigns (Joint Commission, Institute for Safe Medication Practices, and the Food and Drug Administration) to eliminate use of trailing zeros when communicating drug information should help to further reduce risk of medication error.
Fiorinal (C-III)	Orthographic similarity ("T" vs. "F") and ("-imet" vs. "-inal") Potential numerical overlap in strengths (50 mg in Fiorinal vs. 500 mg in Treximet). Overlap could be exacerbated if a trailing zero (e.g. 50.0) is included and the Fiorinal dose or strength is written as 50.0 mg). Note: Fiorinal is available in a 325 mg/40 mg/50 mg strength tablet.	Orthographic differences in the names minimize the likelihood of medication error in the usual practice setting. *Rationale:* The risk for medication error is minimized by the orthographic differences between the names. The beginning letters ("Trex-" vs. "Fior") look different. The potential for overlap exists if the strength or dose of Treximet is written as "500 mg" and Fiorinal is written as "50.0 mg". However, neither Treximet nor Fiorinal is likely to be ordered in this manner because the products contain multiple ingredients. The strength of either product could be omitted and the dose specified as "1 tablet". In the case of Fiorinal, the frequency of administration (every 4 to 6 hours) will also help to differentiate the products since it does not overlap with that of Treximet. The frequency of administration would likely be specified on a Fiorinal prescription since it is a controlled substance and there is a maximum recommended daily dose. Furthermore, usual practice would not typically involve the inclusion of trailing zeros, though medication errors have been linked to this dangerous habit. Numerous campaigns

		(Joint Commission, Institute for Safe Medication Practices, and the Food and Drug Administration) to eliminate use of trailing zeros when communicating drug information should help to further reduce risk of medication error.

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