CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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PROPRIETARY NAME REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Proprietary Name Review

Date:	April 15, 2014
Reviewer:	Rachna Kapoor, PharmD Division of Medication Error Prevention and Analysis
Team Leader:	Yelena Maslov, PharmD Division of Medication Error Prevention and Analysis
Drug Name and Strength(s):	Envarsus XR (Tacrolimus) Extended-Release Tablets, 0.75 mg, 1 mg, and 4 mg
Application Type/Number:	NDA 206406
Applicant/Sponsor:	Veloxis Pharmaceuticals
OSE RCM #:	2014-16828

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

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1 INTRODUCTION

This review evaluates the proposed proprietary name, Envarsus XR, from a safety and promotional perspective. The sources and methods used to evaluate the proposed name are outlined in the reference section and Appendix A respectively.

1.1 REGULATORY HISTORY

The Applicant submitted a request for proprietary name, Envarsus, on January 23, 2014. On March 14, 2014, DMEPA recommended to the Applicant that a modifier be added to the proposed proprietary name, Envarsus, to differentiate it from immediate-release tacrolimus formulations. On March 21, 2014, the Applicant submitted an amendment to the request for proprietary name to add the modifier 'XR'. The proposed proprietary name being evaluated in this review is Envarsus XR. There were no external name studies for this proprietary name.

1.2 PRODUCT INFORMATION

The following product information is provided in the January 23, 2014 proprietary name submission.

- Intended Pronunciation: en var' sus XR
- Active Ingredient: tacrolimus
- Indication of Use: prophylaxis of organ rejection in patients receiving a kidney transplant
- Route of Administration: oral
- Dosage Form: extended-release tablets
- Strength: 0.75 mg, 1 mg, and 4 mg
- Dose and Frequency: 0.17 mg/kg by mouth once daily at the same time
- How Supplied: 30 and 100 count bottles
- Storage: store at 25°C (77°F); excursions permitted to 15°C – 30°C (59°F – 86°F)

2 RESULTS

The following sections provide information obtained and considered in the overall evaluation of the proposed proprietary name.

2.1 PROMOTIONAL ASSESSMENT

The Office of Prescription Drug Promotion OPDP determined the proposed name is acceptable from a promotional perspective. DMEPA and the Division of Transplant and Ophthalmology Products concurred with the findings of OPDP's promotional assessment of the proposed name.

2.2 SAFETY ASSESSMENT

The following aspects were considered in the safety evaluation of the name.

2.2.1 United States Adopted Names (USAN) SEARCH

The January 30, 2014 search of the United States Adopted Name (USAN) stems did not identify that a USAN stem is present in the proposed proprietary name.

2.2.2 Components of the Proposed Proprietary Name

The proposed proprietary name contains two components 1) the proposed root name, Envarsus and 2) the modifier XR. The Applicant indicated in their submission that the proposed root name, Envarsus, has no derivation and the modifier 'XR' is intended to mean extended release. See Section 2.2.6 for further evaluation of the modifier 'XR'.

2.2.3 FDA Name Simulation Studies

One hundred and seven practitioners participated in DMEPA's prescription studies. The interpretations did not overlap with any currently marketed products nor did the misinterpretations sound or look similar to any currently marketed products or any products in the pipeline.

In the written outpatient study, 21 of 37 participants correctly interpreted the prescription. Common misinterpretations in the written outpatient study were substitution of 'e' and 'i' for 's'. In the written inpatient study, 15 of 36 participants correctly interpreted the prescription. Common misinterpretations in the written inpatient study were substitution of 's' for 'v', 'i' for 'r', and 'b' for 'rs'. In the voice study, 2 of 34 participants correctly interpreted the prescription. One common misinterpretation in the voice study included 'y' for 'u'.

We have considered these variations in our look-alike and sound-alike searches and analysis (see Appendix B). See Appendix C for the complete listing of interpretations from the verbal and written prescription studies.

2.2.4 Comments from Other Review Disciplines at Initial Review

In response to the OSE, February 11, 2014 e-mail, the Division of Transplant and Ophthalmology Products (DTOP) forwarded a concern relating to the proposed proprietary name at the initial phase of the review. This extended-release product should have a modifier such as 'XL' to differentiate it from the currently marketed immediate-release tacrolimus product.

2.2.5 Failure Mode and Effects Analysis of Similar Names

Appendix B lists possible orthographic and phonetic misinterpretations of the letters appearing in the proposed proprietary name, Envarsus XR. Table 1 lists the names with orthographic, phonetic, or spelling similarity to the proposed proprietary name, Envarsus XR identified by the primary reviewer, the Expert Panel Discussion (EPD), and other review disciplines.

Table 1: Collective List of Potentially Similar Names (DMEPA, Expert Panel Discussion (EPD), Other Disciplines, and External Name Study)					
Name	***Source***	***Name***	***Source***	***Name***	***Source***
Look Similar					
Femara	FDA	Envigor	FDA	Invanz	FDA
Emtriva	FDA	Inversine	FDA	Invagesic	FDA
Sound Similar					
Narvox	FDA				
Look and Sound Similar					
Omnaris	FDA	Invirase	FDA	Erwinaze	FDA
Ivarest	FDA	(b) (4)	FDA	Invokana	FDA

Our analysis of the thirteen names contained in Table 1 considered the information obtained in the previous sections along with their product characteristics. We determined thirteen names will not pose a risk for confusion as described in Appendices D through E.

2.2.6 Analysis of Modifier XR

Our evaluation of the name Envarsus XR considered whether a modifier is necessary for this product. According to the Applicant, Envarsus XR is an extended-release tablet that should be administered once daily. Currently there are other extended-release and immediate-release tacrolimus products available on the market. The immediate-release tacrolimus products in the marketplace are typically administered twice daily. The extended-release product in the marketplace (i.e., Astagraf XL) is administered once daily. We determined the Applicant needs a modifier based on the following:

This product should be differentiated from immediate-release tacrolimus formulations in terms of nomenclature and not just through labels and labeling because of the differences in frequency of administration (i.e., Tacrolimus Extended-Release product should be administered once daily vs. Tacrolimus Immediate-Release product should be administered twice-daily). Furthermore, both Prograf and Envarsus XR have an overlap in 1 mg strength. As a result, the modifier will serve as an additional indicator that this product should not be used interchangeably with Prograf. Furthermore, post-marketing medication errors have identified cases of chewing, splitting, and crushing of extended-release products. In some cases, the reporters indicate they were unaware the product was extended-release. Addition of the modifier may minimize some of these errors.

Although the modifier 'XR' is different from the modifier used for another extended-release tacrolimus product, Astagraf XL, this difference is not significant, because both modifiers 'XL' and 'XR' are consistently used for extended-release products that should be administered once-daily.

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We recognize there are limitations to the modifier approach since there is post-marketing evidence that modifiers have been omitted or overlooked; however, given the risks associated with confusing this product with the immediate-release products, we believe a modifier signaling the extended-release properties of this drug adds an incremental measure of safety.

For the aforementioned reasons, we conclude the modifier 'XR' is appropriate for this product.

2.2.7 Communication of DMEPA's Analysis at Midpoint of Review

DMEPA communicated our findings to the Division of Transplant and Ophthalmology Products via e-mail on April 1, 2014. At that time we also requested additional information or concerns that could inform our review. Per e-mail correspondence from the Division of Transplant and Ophthalmology Products on April 9, 2014, they stated no additional concerns with the proposed proprietary name, Envarsus XR.

3 CONCLUSIONS

The proposed proprietary name is acceptable from both a promotional and safety perspective.

If you have further questions or need clarifications, please contact Karen Townsend, OSE project manager, at 301-796-5413.

3.1 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Envarsus XR, and have concluded that this name is acceptable.

If any of the proposed product characteristics as stated in your January 23, 2014 submission are altered, the name must be resubmitted for review.

4 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. This database also lists the orphan drugs.

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

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

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

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

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

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

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

   USPTO provides information regarding patent and trademarks.

8. ***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.

9. ***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.

10. ***Access Medicine (www.accessmedicine.com)***

    Access Medicine® from McGraw-Hill contains full-text information from approximately 60 titles; it includes tables and references. Among the titles are: Harrison's Principles of Internal Medicine, Basic & Clinical Pharmacology, and Goodman and Gilman's The Pharmacologic Basis of Therapeutics.

11. ***USAN Stems (http://www.ama-assn.org/ama/pub/about-ama/our-people/coalitions-consortiums/united-states-adopted-names-council/naming-guidelines/approved-stems.shtml)***

    USAN Stems List contains all the recognized USAN stems.

12. ***Red Book (www.thomsonhc.com/home/dispatch)***

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

13. ***Lexi-Comp (www.lexi.com)***

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

14. ***Medical Abbreviations (www.medilexicon.com)***

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

15. ***CVS/Pharmacy (www.CVS.com)***

    This database contains commonly used over the counter products not usually identified in other databases.

16. ***Walgreens (www.walgreens.com)***

    This database contains commonly used over the counter products not usually identified in other databases.

17. ***Rx List (www.rxlist.com)***

    RxList is an online medical resource dedicated to offering detailed and current pharmaceutical information on brand and generic drugs.

18. Dogpile (www.dogpile.com)

Dogpile is a Metasearch engine that searches multiple search engines including Google, Yahoo! and Bing, and returns the most relevant results to the search.

19. Natural Standard (http://www.naturalstandard.com)

Natural Standard is a resource that aggregates and synthesizes data on complementary and alternative medicine.

APPENDICES

Appendix A

FDA's Proprietary Name Risk Assessment considers the promotional and safety aspects of a proposed proprietary name. The promotional review of the proposed name is conducted by OPDP. OPDP evaluates proposed proprietary names to determine if they are overly fanciful, so as to misleadingly imply unique effectiveness or composition, as well as to assess whether they contribute to overstatement of product efficacy, minimization of risk, broadening of product indications, or making of unsubstantiated superiority claims. OPDP provides their opinion to DMEPA for consideration in the overall acceptability of the proposed proprietary name.

The safety assessment is conducted by DMEPA. DMEPA staff search a standard set of databases and information sources to identify names that are similar in pronunciation, spelling, and orthographically similar when scripted to the proposed proprietary name. Additionally, we consider inclusion of USAN stems or other characteristics that when incorporated into a proprietary name may cause or contribute to medication errors (i.e., dosing interval, dosage form/route of administration, medical or product name abbreviations, names that include or suggest the composition of the drug product, etc.). 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. [1]

Following the preliminary screening of the proposed proprietary name, DMEPA gathers to discuss their professional opinions on the safety of the proposed proprietary name. This meeting is commonly referred to the Center for Drug Evaluation and Research (CDER) Expert Panel discussion. DMEPA also considers other aspects of the name that may be misleading from a safety perspective. DMEPA staff conducts a prescription simulation studies using FDA health care professionals. When provided, DMEPA considers external proprietary name studies conducted by or for the Applicant/Sponsor and incorporates the findings of these studies into the overall risk assessment.

The DMEPA primary reviewer assigned to evaluate the proposed proprietary name 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 misleading nature of the proposed proprietary name with a focus on the avoidance of medication errors.

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. DMEPA considers the product characteristics associated with the proposed product 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.

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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.

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. DMEPA considers how these product characteristics may or may not be present in communicating a product name throughout the medication use system. Because drug name confusion can occur at any point in the medication use process, DMEPA considers the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.[2]

The DMEPA considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. DMEPA compares the proposed proprietary name with the proprietary and established name of existing and proposed drug products and names currently under review at the FDA. DMEPA 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. DMEPA examines the phonetic similarity using patterns of speech. If provided, DMEPA will consider the Sponsor's intended pronunciation of the proprietary name. However, DMEPA also considers a variety of pronunciations that could occur in the English language because the Sponsor has little control over how the name will be spoken in clinical practice. The orthographic appearance of the proposed name is evaluated using a number of different handwriting samples. DMEPA applies expertise gained from root-cause analysis of postmarketing 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).

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

Table 1. Criteria Used to Identify Drug Names that Look- or Sound-Similar to a Proposed Proprietary Name.

Type of Similarity	**Considerations when Searching the Databases**		
	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/Similar shape Upstrokes Down strokes Cross-strokes 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

Lastly, DMEPA 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 searches 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. A standard description of the databases used in the searches is provided in the reference section of this review. To complement the process, the DMEPA uses a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, DMEPA reviews 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. DMEPA also evaluates if there are characteristics included in the composition that may render the name unacceptable from a safety perspective (abbreviation, dosing interval, etc.).

2. Expert Panel Discussion

DMEPA gathers gather CDER professional opinions on the safety of the proposed product and discussed the proposed proprietary name (Expert Panel Discussion). The Expert Panel is composed of Division of Medication Errors Prevention (DMEPA) staff and representatives from the Office of Prescription Drug Promotion (OPDP). We also consider input from other review disciplines (OND, ONDQA/OBP). 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 database and information searches to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend additional 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 Simulation 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 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 record their interpretations of the orders which are recorded electronically.

4. Comments from Other Review Disciplines

DMEPA requests the Office of New Drugs (OND) and/or Office of Generic Drugs (OGD), ONDQA or OBP for their comments or concerns with the proposed proprietary name, ask for any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with OPDP's decision on the name. The primary Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

The OND/OGD Regulatory Division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name. The OND or OGD Regulatory Division is requested to provide any further information that might inform DMEPA's final decision on the proposed name.

Additionally, other review disciplines opinions such as ONDQA or OBP may be considered depending on the proposed proprietary name.

5. 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, considers all aspects of the name that may be misleading or confusing, conducts a Failure Mode and Effects Analysis, and provides an overall decision on acceptability dependent on their 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.[3] 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

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

characteristics listed in Section 1.2 of this review. 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? And are there any components of the name that may function as a source of error beyond sound/look-alike?"***

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 or because of some other component of the name. If the answer to the question is no, the Safety Evaluator is not convinced that the names possess similarity that would cause confusion at any point in the medication use system, thus the name is eliminated from further review.

In the second stage of the Risk Assessment, the primary Safety Evaluator evaluates all potential failure modes to determine the likely *effect* of the drug name confusion, by asking:

> ***"Could the confusion of the drug names conceivably result in medication errors in the usual practice setting?"***

The answer to this question is a central component of the Safety Evaluator's overall risk assessment of the proprietary name. If the Safety Evaluator determines through FMEA that the name similarity would not ultimately be a source of medication errors in the usual practice setting, the primary Safety Evaluator eliminates the name from further analysis. However, if the Safety Evaluator determines through FMEA that the name similarity could ultimately cause medication errors in the usual practice setting, the Safety Evaluator will then recommend the use of an alternate proprietary name.

Moreover, 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 Overall Risk Assessment:

a. OPDP finds the proposed proprietary name misleading from a promotional perspective, and the Review Division concurs with OPDP'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 but involve a naming characteristic that when incorporated into a proprietary name, may be confusing, misleading, cause or contribute to medication errors.

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 generally recommends 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. In that instance, DMEPA may be able to provide the Sponsor with recommendations that reduce or eliminate the potential for error and, thereby, would render the proposed name acceptable.

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

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

Furthermore, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to rectify post-approval. Educational and other post-approval efforts are low-leverage strategies that have had limited effectiveness at alleviating medication errors involving drug name confusion. Sponsors have undertaken higher-leverage strategies, such as drug name changes, in the

past but at great financial cost to the Sponsor and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for approving the error-prone proprietary name. Moreover, even after Sponsors' have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioners' vocabulary, and as a result, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, DMEPA believes that post-approval efforts at reducing name confusion errors should be reserved for those cases in which the potential for name confusion could not be predicted prior to approval.

Appendix B: Letters and Letter Strings with Possible Orthographic or Phonetic Misinterpretation

Letters in Name Envarsus XR	**Scripted May Appear as**	**Spoken May Be Interpreted as**
Capital 'E'	C, f, I	any vowel
Lower case 'e'	a, i, l, o, u, p	any vowel
Lower case 'n'	m, u, x, r, h, s, v	dn, gn, kn, mn, pn, m
Lower case 'v'	r, u, w, s	f
Lower case 'a'	el, ci, cl, d, o, u, e	any vowel
Lower case 'r'	s, n, e, v, z, i	--
Lower case 's'	G, 5, g, n, r, re, e, i	x, c
Lower case 'u'	n, y, v, w	any vowel, y
Capital 'X'	d, f, K, P, t, U, V, Y	KS, KZ, S, Z
Capital 'R'	B, Pr, K	WR
Letter strings in Name Envarsus XR	**Scripted May Appear as**	**Spoken May Be Interpreted as**
nv	lw, mi	--
rs	b	--

Appendix C: Prescription Simulation Samples and Results

Figure 1. Envarsus XR Study (Conducted on March 28, 2014)

Handwritten Requisition Medication Order	Verbal Prescription
Medication Order: Envarsus XR 12mg by mouth once daily	Envarsus XR Take 12 mg by mouth once daily Dispense: #90
Outpatient Prescription: Envarsus XR 12mg po qd #90	

FDA Prescription Simulation Responses (Aggregate 1 Rx Studies Report)

Study Name: Envarsus XR

As of Date 4/8/2014

276 People Received Study

107 People Responded

Total	37	34	36	
INTERPRETATION	**OUTPATIENT**	**VOICE**	**INPATIENT**	**TOTAL**
ADVARSIS XR	0	1	0	1
ENARSUS XR	0	0	1	1
ENIABUS XR	0	0	1	1
ENIVARSUS XR	0	0	1	1
ENRARSUS XR	0	0	1	1
ENSABUS XR	0	0	2	2
ENSARSUS XR	0	0	1	1
ENVABUS XR	0	0	1	1
ENVAISUS XR	0	0	4	4
ENVARCIS XR	0	1	0	1
ENVARESUS XR	1	0	0	1
ENVAREUS XR	5	0	0	5
ENVARIUS	1	0	0	1
ENVARIUS XR	3	0	0	3
ENVARSES XR	0	1	0	1
ENVARSESS SR	0	1	0	1
ENVARSESS XR	0	1	0	1
ENVARSIS XR	0	14	0	14
ENVARSUE XR	0	0	1	1

ENVARSUS	1	0	0	1
ENVARSUS XR	21	2	15	38
ENVARSUS XT	0	0	1	1
ENVARUE XR	0	0	1	1
ENVARUS XR	1	0	1	2
ENVARXSUS XR	0	1	0	1
ENVASERF XR	0	1	0	1
ENVASIS XR	0	1	0	1
ENVASUE XR	0	0	2	2
ENVASUS XR	0	0	1	1
ENVORRUS XR	1	0	0	1
ENVORSUS XR	1	0	0	1
ERIARSUS XR	0	0	1	1
EURARSUS XR	0	0	1	1
EUVARSUS XR	1	0	0	1
EUVASRSUS XR	1	0	0	1
INVARCIS XR	0	1	0	1
INVARSIS SR	0	1	0	1
INVARSIS XR	0	5	0	5
INVARSUS SR	0	1	0	1
INVARSYS XR	0	1	0	1
INVULSIVE XR	0	1	0	1

Appendix D: Proprietary names not likely to be confused or not used in usual practice settings for the reasons described.

No.	Proprietary Name	Active Ingredient	Similarity to Envarsus	Failure preventions
1	Femara	Letrozole	Look	The pair has sufficient orthographic differences
2	Emtriva	Emtricitabine	Look	The pair has sufficient orthographic differences
3	Narvox	Acetaminophen and oxycodone hydrochloride	Sound	The pair has sufficient phonetic differences
4	Omnaris	Ciclesonide	Look and sound	The pair has sufficient orthographic and phonetic differences
5	(b) (4)	Calasparagase pegol	Look and sound	The name was denied due to (b) (4)

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

Appendix E: Risk of medication errors due to product confusion minimized by dissimilarity of the names and/ or use in clinical practice for the reasons described.

	Proposed name: ***Envarsus*** (Tacrolimus) **Dosage form and Strength(s):** Extended-release tablets: 0.75 mg, 1 mg, and 4 mg **Usual dose:** 0.17 mg/kg by mouth once daily at the same time (for a 70 kg patient, dose is 11.9 mg)	**Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion** **Causes (could be multiple)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
1	**Invanz** (Ertapenem sodium) **Dosage form and Strength:** Powder for injection: 1 g **Usual dose:** 1 g intravenously or intramuscularly once a day	**Orthographic similarities:** The prefix 'Invan' in Invanz looks orthographically similar to the prefix 'Envar' in Envarsus when scripted. **Product characteristics similarities:** Strength and dose: there is overlap in strength – tacrolimus 1 mg vs. ertapenem sodium 1,000 mg (1 g) In addition, the dose can numerically overlap – tacrolimus 10 mg vs. ertapenem sodium 1 g	**Orthographic differences:** The shape and length of both names is different. Invanz is shorter than Envarsus. The ending 'z' in Invanz looks orthographically different than the ending 'sus' in Envarsus.

	Proposed name: ***Envarsus*** (Tacrolimus) **Dosage form and Strength(s):** Extended-release tablets: 0.75 mg, 1 mg, and 4 mg **Usual dose:** 0.17 mg/kg by mouth once daily at the same time (for a 70 kg patient, dose is 11.9 mg)	**Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion** **Causes (could be multiple)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
2	**Envigor** (Ascorbic acid 60 mg, biotin 300 mcg, calcium 260 mg, cyanocobalamin 6 mcg, ginkgo biloba 120 mg, ginseng 200 mg, niacin 20 mg, pantothenic acid 10 mg, pyridoxine 2 mg, riboflavin 1.7 mg, thiamine 1.5 mg, and vitamin E 30 units) **Dosage form:** Oral tablet **Usual dose:** Take one tablet by mouth as needed	**Orthographic similarities:** Both names start with the same prefix 'Env' and have a similar length. **Product characteristics similarities:** Dose: the numerical dose can overlap – tacrolimus 10 mg vs. Envigor 1 tablet	**Orthographic differences:** The ending 'igor' in Envigor looks orthographically different than the ending 'arsus' in Envarsus when scripted. The letter 'g' in the 5th position of Envigor has a downstroke, which is not present in Envarsus.
3	**Inversine** (Mecamylamine hydrochloride) **Dosage form and Strength:** Oral tablet: 2.5 mg **Usual dose:** One tablet by mouth twice a day	**Orthographic similarities:** Both names have a similar length and shape. The prefix 'Invers' in Inversine looks orthographically similar to the prefix 'Envars' in Envarsus when scripted.	**Orthographic differences:** The ending 'ine' in Inversine looks orthographically different from the ending 'us' in Envarsus when scripted. **Product characteristics differences:** Strength: the strengths do not overlap Dose: the doses do not overlap

	Proposed name: ***Envarsus*** (Tacrolimus) **Dosage form and Strength(s):** Extended-release tablets: 0.75 mg, 1 mg, and 4 mg **Usual dose:** 0.17 mg/kg by mouth once daily at the same time (for a 70 kg patient, dose is 11.9 mg)	**Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion** **Causes (could be multiple)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
4	**Erwinaze** (Asparaginase) **Dosage form and Strength:** Powder for injection: 10,000 units **Usual dose:** 25,000 units/m^2 intramuscularly three times a week for 6 doses (for a patient 1.6 m^2, dose is 40,000 units)	**Orthographic similarities:** Both names have a similar length. The prefix 'Erw' in Erwinaze looks orthographically similar to the prefix 'Env' in Envarsus when scripted. **Phonetic similarities:** Both names have 3 syllables.	**Orthographic differences:** Both names have a different shape. The letter 'z' in the 7th position of Erwinaze has a downstroke, which is not present in Envarsus. The ending 'inaze' in Erwinaze looks orthographically different than the ending 'arsus' in Envarsus when scripted. **Phonetic differences:** All three syllables give the names a distinctly different sound when spoken ('er' vs. 'en' and 'win' vs. 'var' and 'aze' vs. 'sus'). **Product characteristics differences:** Strength: the strengths do not overlap Dose: the doses do not overlap

	Proposed name: ***Envarsus*** (Tacrolimus) **Dosage form and Strength(s):** Extended-release tablets: 0.75 mg, 1 mg, and 4 mg **Usual dose:** 0.17 mg/kg by mouth once daily at the same time (for a 70 kg patient, dose is 11.9 mg)	**Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion** **Causes (could be multiple)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
5	**Invirase** (Saquinavir mesylate) **Dosage form and Strength(s):** Oral capsule: 200 mg Oral tablet: 500 mg **Usual dose:** 1,000 mg by mouth twice daily with ritonavir	**Orthographic similarities:** Both names have a similar length and shape. The prefix 'Inv' in Invirase looks orthographically similar to the prefix 'Env' in Envarsus when scripted. **Phonetic similarities:** Both names have 3 syllables. The first and second syllables in both names sound similar when spoken ('in' vs. 'en' and 'vir' vs. 'var'). **Product characteristics similarities:** Strength and dose: the numerical dose can overlap – tacrolimus 10 mg vs. saquinavir mesylate 1,000 mg (1 g)	**Orthographic differences:** The ending 'irase' in Invirase looks orthographically different than the ending 'arsus' in Envarsus when scripted. **Phonetic differences:** The third syllable in both names gives the names a distinctly different sound when spoken ('ase' vs. 'sus').

	Proposed name: ***Envarsus*** (Tacrolimus) **Dosage form and Strength(s):** Extended-release tablets: 0.75 mg, 1 mg, and 4 mg **Usual dose:** 0.17 mg/kg by mouth once daily at the same time (for a 70 kg patient, dose is 11.9 mg)	**Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion** **Causes (could be multiple)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
6	**Invagesic** (Aspirin, caffeine, and orphenadrine citrate) **Dosage form and Strength:** Extended-release tablet: aspirin 385 mg / caffeine 30 mg / orphenadrine citrate 25 mg **Usual dose:** One to two tablets by mouth three to four times daily	**Orthographic similarities:** Both names have a similar length. The prefix 'Inva' in Invagesic looks orthographically similar to the prefix 'Enva' in Envarsus when scripted. **Phonetic similarities:** The first syllable in both names sounds similar when spoken ('in' vs. 'en'). **Product characteristics similarities:** Dose: the numerical dose can overlap – tacrolimus 10 mg vs. Invagesic 1 tablet	**Orthographic differences:** Both names have a different shape. The letter 'g' in the 5th position of Invagesic has a downstroke, which is not present in Envarsus. The ending 'gesic' in Invagesic looks orthographically different than the ending 'rsus' in Envarsus when scripted. **Phonetic differences:** Invagesic has 4 syllables vs. Envarsus which has 3 syllables. The remaining syllables in both names give the names a distinctly different sound when spoken ('va', 'ges', 'ic' vs. 'var', 'sus'). This ANDA 074817 was approved on November 27, 1996. On January 16, 2014, the Sponsor (Sandoz) stated that they are not currently manufacturing or marketing this product. The product is currently listed in the discontinued section of the Orange Book.

	Proposed name: ***Envarsus*** (Tacrolimus) **Dosage form and Strength(s):** Extended-release tablets: 0.75 mg, 1 mg, and 4 mg **Usual dose:** 0.17 mg/kg by mouth once daily at the same time (for a 70 kg patient, dose is 11.9 mg)	**Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion** **Causes (could be multiple)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
7	**Ivarest** (Calamine, benzyl alcohol, and diphenhydramine hydrochloride) **Dosage form and Strength:** Topical cream: calamine 14%, benzoyl alcohol 10.5%, and diphenhydramine hydrochloride 2% Cleansing foam: strength not indicated **Usual dose:** Apply to affected area not more than 3 to 4 times daily	**Orthographic similarities:** Both names have a similar length. The first letter 'I' in Ivarest looks orthographically similar to the first letter 'E' in Envarsus when scripted. Both names have the infix 'var'. **Phonetic similarities:** Both names have 3 syllables.	**Orthographic differences:** Both names have a different shape. Ivarest ends with the letter 't' which has an upstroke. The ending 'est' in Ivarest looks orthographically different than the ending 'sus' in Envarsus when scripted. **Phonetic differences:** All three syllables give the names a distinctly different sound when spoken ('i' vs. 'en' and 'va' vs. 'var' and 'rest' vs. 'sus'). **Product characteristics differences:** Strength: the strengths do not overlap Dose: the doses do not overlap POCA has Invarest with combined score of 72% (RxNorm). Product characteristics for Invarest are not available on any major databases. The search results in product characteristics for Ivarest.

	Proposed name: ***Envarsus*** (Tacrolimus) **Dosage form and Strength(s):** Extended-release tablets: 0.75 mg, 1 mg, and 4 mg **Usual dose:** 0.17 mg/kg by mouth once daily at the same time (for a 70 kg patient, dose is 11.9 mg)	**Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion** **Causes (could be multiple)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
8	**Invokana** (Canagliflozin) **Dosage form and Strength:** Oral tablet: 100 mg and 300 mg **Usual dose:** 100 mg by mouth once daily, taken before the first meal of the day. The dose can be increased to 300 mg by mouth once daily in those who require additional glycemic control	**Orthographic similarities:** Both names have a similar length. The prefix 'Invo' in Invokana looks orthographically similar to the prefix 'Enva' in Envarsus when scripted. **Phonetic similarities:** The first syllable in both names sounds similar when spoken ('in' vs. 'en'). **Product characteristics similarities:** Strength and dose: there is overlap in strength – tacrolimus 1 mg vs. canagliflozin 100 mg In addition, the dose can numerically overlap – tacrolimus 10 mg vs. canagliflozin 100 mg	**Orthographic differences:** Both names have a different shape. The letter 'k' in the 5th position of Invokana has an upstroke, which is not present in Envarsus. The ending 'kana' in Invokana looks orthographically different than the ending 'rsus' in Envarsus when scripted. **Phonetic differences:** Invokana has 4 syllables vs. Envarsus which has 3 syllables. The remaining syllables in both names give the names a distinctly different sound when spoken ('vo', 'kan', 'a' vs. 'var', 'sus').

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/s/

RACHNA KAPOOR
04/15/2014

YELENA L MASLOV
04/15/2014

LUBNA A MERCHANT
04/15/2014