CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-560

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:	January 11, 2009
To:	Renata Albrecht, MD Director, Division of Special Pathogen and Transplant Products
Through:	Carlos Mena-Grillasca, RPh, Team Leader Denise Toyer, PharmD, Deputy Director Kellie Taylor, PharmD, MPH, Associate Director Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis
From:	Judy Park, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Proprietary Name Review
Drug Name(s):	Zortress (Everolimus) Tablets
	0.25 mg, 0.5 mg, 0.75 mg, and 1 mg
Application Type/Number:	NDA 021560
Applicant:	Novartis
OSE RCM #:	2009-2004

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

CONTENTS

EXECUTIVE SUMMARY

Zortress is the proposed proprietary name for everolimus tablets. Everolimus tablets are currently marketed by the same Applicant for a different indication of use under a different proprietary name. Thus, Zortress represents a dual proprietary name for this product from the same Applicant. This proposed name was evaluated from a safety and promotional perspective based on the product characteristics provided by the Applicant. We sought input from pertinent disciplines involved with the review of this application and considered it accordingly. Considering the use of a dual proprietary name and other aspects of the proposed name, our evaluation did not identify concerns that would render the name unacceptable based on the product characteristics and safety profile known at the time of this review. Our assessment supports the findings of the External Proprietary Name Risk Assessments submitted by the Applicant. Thus, DMEPA finds the proposed proprietary name, Zortress, acceptable for this product. The proposed proprietary name must be re-reviewed 90 days before approval of the drug.

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

1 BACKGROUND

1.1 INTRODUCTION

This review is written in response to a request from Novartis for assessment of the proposed proprietary name, Zortress, regarding its potential confusion with other proprietary or established drug names in normal practice settings.

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

1.2 REGULATORY HISTORY

(b) (4)

The Applicant submitted an alternate proposed name, Zortress, for review and comment.

Zortress is a dual-trade name request. Everolimus tablets are already marketed as Afinitor by the same Applicant for a different indication.

1.3 PRODUCT INFORMATION

Zortress (everolimus) is indicated for the prophylaxis of organ rejection in adult patients at low to moderate immunological risk receiving an allogenic renal transplant. It should be used in combination with cyclosporine USP Modified and corticosteroids. Everolimus is already marketed by the same Applicant under the proprietary name, Afinitor, which was approved in March 2009. See Table 1 for the product characteristic differences between the two products. Zortress is available in 0.25 mg, 0.5 mg, 0.75 mg, and 1 mg oral tablet. The dose is 1.5 mg/day to 3 mg/day.

Table 1: Summary of Product Characteristics of Zortress and Afinitor

	Zortress (NDA 021560)	**Afinitor (NDA 022334)**
Indication	Prophylaxis of organ rejection in adult patients at low to moderate immunological risk receiving an allogenic renal transplant. It should be used in combination with cyclosporine USP Modified and corticosteroids.	Treatment of patients with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib.
Strength	0.25 mg, 0.5 mg, 0.75 mg, 1 mg	2.5 mg*, 5 mg, 10 mg
Dose	1.5 mg/day to 3 mg/day	5 mg to 10 mg
Dosage Form	Oral Tablet	Oral Tablet
Frequency of Administration	Twice daily	Once daily
How Supplied	6 cards with 10 tablets per card	28 tablets/package; 2 blisters of 14 tablets per blister
Tablet Shape	Round	Elongated
Tablet side 1	C, CH, CL, CU	2.5, 5, UHE
Tablet side 2	NVR	NVR
Patient Monitoring	Whole blood trough levels	Not anticipated

2 METHODS AND MATERIALS

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

2.1 SEARCH CRITERIA

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

For this review, particular consideration was given to drug names beginning with the letter 'Z' when searching to identify potentially similar drug names, as 75% of the confused drug names reported by the USP-ISMP Medication Error Reporting Program involve pairs beginning with the same letter.[1,2]

---

* 2.5 mg tablet is not yet marketed but was agreed to be pursued with the Agency to assist in titration needs

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

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

To identify drug names that may look similar to Zortress, the DMEPA staff also consider the orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (eight letters), upstrokes (two, capital letters 'Z' and 't'); downstokes (one, lower case 'z'), cross-strokes (lower case 't'), and dotted letters (none). Additionally, several letters in Zortress may be vulnerable to ambiguity when scripted, including the letter 'Z' may appear as 'L,' or 'r'; lower case 't' may appear as 'x'; lower case 'r' may appear as 'n'; lower case 's' may appear as lower case lower case 'r'; lower case 'o' and 'e' may appear as any of the vowels. As such, the DMEPA staff also considers these alternate appearances when identifying drug names that may look similar to Zortress.

When searching to identify potential names that may sound similar to Zortress, DMEPA staff searches for names with similar number of syllables (two), stresses (ZOR-tress, zor-TRESS), and placement of vowel and consonant sounds. Additionally, several letters in Zortress may be vulnerable to misinterpretation when spoken, including 'Z' may be interpreted as 'C,' 'J,' or 'S'; 's' may be interpreted as 'ce'; and 'e' may be interpreted as 'eh' or 'i'. As such, the staff also considers these alternate pronunciations when identifying drug names that may sound similar to Zortress. The Applicant's intended pronunciation of the proprietary name could not be expressly taken into consideration, as this was not provided with the proposed name submission.

2.2 FDA PRESCRIPTION ANALYSIS STUDIES

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

Figure 1. Zortress Rx Study (conducted on October 30, 2009)

HANDWRITTEN REQUISITION MEDICATION ORDER	VERBAL PRESCRIPTION
Inpatient Medication Order : Zortress 0.75mg po BID	Zortress 0.75 mg 1 tab twice daily #60
Outpatient Prescription: Zortress 0.75mg #60 1 po bid	

3 RESULTS

3.1 DATABASE AND INFORMATION SOURCES

The searches yielded a total of 24 names as having some similarity to the name, Zortress.

Twenty of the 24 names were thought to look like Zortress. These names are Clorpres, Fentuss, Lactrase, Lantus, (b) (4) Lortab, Lortruss DM, Lortruss, HC, Lortuss DM, Lortuss HC, Ocupress, Nortrel,

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

Solotuss, Zartan (b) (4) Zerit, Zestril, Zofran, Zorbitive, and Zorbtive. One of the 24 names (Zotex) was thought to sound like Zortress. Three of the 24 names (Isentress, Zortrix and Zostrix) were thought to both look and sound like Zortress.

DMEPA staff did not identify any United States Adopted Names (USAN) stems in the proposed proprietary name, as of November 10, 2009.

3.2 EXPERT PANEL DISCUSSION

The Expert Panel reviewed the pool of names identified by DMEPA staff (See Section 3.1 above) and noted no additional names thought to have orthographic or phonetic similarity to Zortress.

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

3.3 FDA PRESCRIPTION ANALYSIS STUDIES

A total of 22 practitioners responded to the prescription analysis studies, but none of the responses overlapped with any existing or proposed drug names. Thirteen respondents interpreted the name correctly as Zortress. The remainder of the respondents (n=9) misinterpreted the drug name, primarily because 'o' was misinterpreted as 'a'; or 'Zort' was misinterpreted as 'Zot' in the written studies; 'Z' was misinterpreted as 'S'; '-tress' was misinterpreted as 'dtrus' or '-tres'; and 'e' was misinterpreted as 'a' in the verbal study. See Appendix B for the complete listing of interpretations from the verbal and written prescription studies.

3.4 EXTERNAL PROPRIETARY NAME RISK ASSESSMENTS

The Applicant submitted an independent risk assessment of the name, Zortress, conducted by a consulting firm, (b) (4) and an independent risk assessment of dual proprietary naming conducted by a consulting firm, (b) (4) evaluated dual trade names, Certican (b) (4) (b) (4) and Afinitor (currently marketed product by the same Applicant). (b) (4) evaluated the proprietary name, Zortress and its potential for name confusion.

In the proposed name risk assessment of Zortress (b) (4) identified and evaluated two names thought to have some potential for confusion with the name Zortress: Motrin and Zostrix. Of the two names, DMEPA also identified Zostrix during the database searches. The name, Motrin, will be added to the Safety Evaluator Assessment (b) (4) analysis determined that there are no significant look-alike or sound-alike drug names or medical terms to Zortress and overall, the proposed proprietary name, Zortress, has low vulnerability for confusion from a safety standpoint.

(b) (4) assessment of dual proprietary naming for everolimus concluded in favor of the use of two separate proprietary names for the two indications (see Section 4 *Discussion*).

3.5 COMMENTS FROM THE REVIEW DIVISIONS

3.5.1 Initial Phase of Review

In a response to the OSE October 29, 2009 e-mail, the Division of Special Pathogen and Transplant Products (DSPTP) did not object to the proposed proprietary name, Zortress. The Review Division also did not express any safety concerns with the Applicant's proposal for a dual trade name for everolimus per November 18, 2009 e-mail.

3.5.2 Midpoint of Review

On December 8, 2009, DMEPA notified DSPTP via e-mail that we had no objections to the proposed proprietary name Zortress. Per e-mail correspondence from DSPTP on December 9, 2009, they indicated that they concur with our assessment of the proposed proprietary name, Zortress.

On December 16, 2009, DMEPA also notified the Division of Drug Oncology Products (DDOP) via e-mail that we found no objections to the proposed proprietary name, Zortress. Per e-mail correspondence on January 5, 2010, DDOP indicated that they had no clinical concerns with the proposed name, Zortress.

3.6 SAFETY EVALUATOR RISK ASSESSMENT

Independent searches by the primary Safety Evaluator did not result in any additional names thought to look similar to Zortress and represent a potential source of drug name confusion.

Upon further observation, two of the 25 names (Lortruss DM and Lortruss HC) were found to be misspelling of the names, Lortuss DM and Lortuss HC, which were also identified in the database searches. Therefore, the mispelled names were eliminated from further analysis.

Thus, we evaluated a total of 23 names for their similarity to the proposed name and considered the use of Zortress as a dual proprietary name for this product.

4 DISCUSSION

The proposed Zortress (everolimus) tablets product will be an extension of the everolimus product line manufactured by Novartis and marketed under the proprietary name Afinitor. In addition to having the same active ingredient as Afinitor, Zortress will have numerically similar strengths to Afinitor: (0.25 mg vs. 2.5 mg, 0.5 mg vs. 5 mg and 1 mg vs. 10 mg), the same dosage form (tablets) and the same route of administration (oral) . A primary difference between Zortress and Afinitor is that Zortress is proposed to be indicated for the prophylaxis of organ rejection while Afinitor is indicated as treatment for advanced renal cell carcinoma. Zortress therapy will also require therapeutic drug monitoring (whole blood trough) levels) and will be dosed twice daily, while Afinitor does not require therapeutic drug monitoring and is dosed once daily. See chart on page 4 for a comparison of Zortress and Afinitor characteristics.

The Applicant proposes a new and different proprietary name for this product. In evaluating this proprietary name, we considered whether the product could be safely managed using the name, Zortress, and considered the risk of inadvertent concomitant administration of the everolimus products.

4.1 EVEROLIMUS PRODUCT LINE EXTENSION

The Applicant proposes to market the new everolimus product under a new proprietary name in order to reduce the risk of confusion between Afinitor and Zortress. Their concern is that both products share numerically similar strengths (0.25 mg vs. 2.5 mg, 0.5 mg vs. 5 mg, and 1 mg vs. 10 mg), a single proprietary name may increase the potential for confusion between these strengths resulting in 10-fold overdoses or underdoses of everolimus. We share this concern since similar mix-ups have been documented with other products that have numerically similar strengths (e.g. Prograf 0.5 mg vs Prograf 5 mg) and have resulted in serious adverse events.[3] DMEPA is concerned that if the '0' in the strength of Zortress is overlooked or omitted a 10-fold overdose of everolimus may be dispensed and administered (e.g. 0.25 mg of everolimus intended, but 2.5 mg everolimus administered). Conversely, DMEPA is concerned that if the decimal point in the strength of Afinitor is overlooked or omitted a 10-fold underdose of everolimus may be dispensed and administered (e.g. intended 2.5 mg of everolimus, but

[3] Duffy, F. OSE Review 2007-2052. 23 Jan 2008

0.25 mg administered). Based on our post-marketing experience with Prograf, we predict that these types of errors are likely to have serious clinical consequences including graft loss or undertreated malignancy.

In considering these potential medication errors, we acknowledge that the use of unique proprietary name for the everolimus product indicated for prophylaxis of organ rejection may help to mitigate some of the potential for confusion between the various everolimus strengths. However, the products will share the same established name (everolimus) and prescribers may use that name when prescribing and ordering the product. A higher-leverage approach to addressing this risk of confusion between the everolimus tablets would have been to develop strengths in numerical increments that do not numerically overlap with the currently marketed Afinitor product (e.g. 0.3 mg, 0.6 mg, 0.8 mg, 1.2 mg) so that if a zero or decimal point was overlooked, the likelihood of dispensing the wrong strength would be greatly reduced.

Additionally, with the use of a new proprietary name, Zortress, there is a risk of concomitant therapy of everolimus if practitioners and patients fail to recognize that both Zortress and Afinitor contain everolimus. The Applicant has acknowledged and considered this risk, and stated that due to the differences in indications, that they believe it is very unlikely that a patient who is receiving Afinitor will receive duplicative therapy of everolimus by being prescribed Zortress (and vice versa) due to the highly specialized patient population of the two indications (oncology and transplant). The Applicant states that a patient being treated for renal cancer (Afinitor) would unlikely be simultaneously treated for kidney transplant (Zortress) and vice versa and thus concludes the likelihood of concomitant administration is minimal.

In considering this risk, we acknowledge that the differing indications may help to minimize the possibility that a patient might require concomitant therapy with Zortress and Afinitor. However, post-marketing experience with other drug products marketed under one or more proprietary names has shown that such differences alone have not prevented medication errors in which patients have inadvertently received two or more products containing the same active ingredient.[4] A number of dual proprietary names are documented sources of medication errors in the clinical setting, including Revatio/Viagra, Zyban/Wellbutrin, Propecia/Proscar and Sarafem/Prozac. Additionally, safety experts note that when the drugs are prescribed by different providers, dispensed by different pharmacies or when a physician prescribes the product by its generic name and it is dispensed and labeled by its proprietary name (e.g. Coumadin or Jantoven for a patient already taking Warfarin); the potential for medication errors is compounded even more. Thus, DMEPA is not convinced that the risk of concomitant therapy is mitigated by the different indications of use alone.

However, we agree overall with the applicant that a different proprietary name may help to reduce the likelihood of strength confusion within the everolimus product line though we anticipate that errors may occur when prescribers order the products using the established name. For this reason, we find the approach of using a dual proprietary name acceptable. We remain concerned about these potential errors in addition to the potential for concomitant therapy. These risks may be further reduced (but not fully eliminated) through labeling (insert, carton, and container) with our recommendations in OSE Review #2009-1240 dated December 23, 2009, and education. Additionally, because we anticipate that medication errors will occur regardless of the proprietary name used and labeling elements employed, DMEPA plans to monitor for such errors after approval of Zortress.

DSPTP and DDOP also did not have any safety concerns regarding the use of a dual proprietary name for everolimus, and the use of a dual proprietary name was supported by the results of an external risk assessment conducted by (b) (4) and submitted by the Applicant.

4.2 ZORTRESS ASSESSMENT OF RISK OUTSIDE THE EVEROLIMUS PRODUCT LINE

[4] The Institute for Safe Medication Practices. "Revatio=Sildenafil=Viagra". January 2009

DDMAC, DSPTP or DDOP did not have concerns with the proposed name, Zortress.

DMEPA identified and evaluated 23 names for their potential similarity to the proposed name. Nine names lacked orthographic and/or phonetic similarity and were not evaluated further (see Appendix C). Failure mode and effect analysis (FMEA) was then applied to determine if the potential name could potentially be confused with the remaining 14 names and lead to medication errors. This analysis determined that the name similarity between Zortress was unlikely to result in medication errors with any of the 14 names for the reasons presented in Appendices D through I.

Thus, DMEPA has no objection to the proprietary name, Zortress. Our assessment supports the findings of the Proprietary Name Risk Assessment conducted by (b) (4) and submitted by the Applicant

5 CONCLUSIONS AND RECOMMENDATIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Zortress, is not vulnerable to name confusion nor is it considered to be promotional.

However, if any of the proposed product characteristics as stated in this review are altered prior to approval of the product, DMEPA rescinds this Risk Assessment finding and the name must be resubmitted for review. In the event that our Risk Assessment finding is rescinded, the evaluation of the name on resubmission is independent of the previous Risk Assessment, and as such, the conclusions on re-review of the name are subject to change. If the approval of this supplement is delayed beyond 90 days from the signature date of this review, the proposed name must be resubmitted for evaluation. If you have further questions or need clarifications, please contact Karen Townsend, OSE Project Manager, at 301-796-5413.

6 REFERENCES

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

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

2. Phonetic and Orthographic Computer Analysis (POCA)

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

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

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

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

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

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

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

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

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

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

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

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

USPTO provides information regarding patent and trademarks.

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

Clinical Pharmacology contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common, combination, nutraceutical and nutritional products. It also provides a keyword search engine.

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

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

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

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

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

Stat!Ref contains full-text information from approximately 30 texts; it includes tables and references. Among the database titles are: Handbook of Adverse Drug Interactions, Rudolphs Pediatrics, Basic Clinical Pharmacology, and Dictionary of Medical Acronyms Abbreviations.

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

USAN Stems List contains all the recognized USAN stems.

14. Red Book Pharmacy's Fundamental Reference

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

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

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

16. Medical Abbreviations Book

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

APPENDICES

Appendix A:

FDA's Proprietary Name Risk Assessment considers the potential for confusion between the proposed proprietary name and the proprietary and established names of drug products existing in the marketplace and those pending IND, NDA, BLA, and ANDA products currently under review by the Center. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [5]

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

The Safety Evaluator assigned to the Proprietary Name Risk Assessment is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name. DMEPA bases

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

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

FMEA is a systematic tool for evaluating a process and identifying where and how it might fail. [6] DMEPA uses FMEA to analyze whether the drug names identified with orthographic or phonetic similarity to the proposed proprietary name could cause confusion that subsequently leads to medication errors in the clinical setting. DMEPA uses the clinical expertise of its staff to anticipate the conditions of the clinical setting where the product is likely to be used based on the characteristics of the proposed product.

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

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed proprietary name include, but are not limited to; established name of the proposed product, proposed indication of use, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. Because drug name confusion can occur at any point in the medication use process, DMEPA staff considers the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.[7] DMEPA provides the product characteristics considered for this review in section one.

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

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

[7] 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 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, the DMEPA staff also considers the potential for the proposed proprietary name to inadvertently function as a source of error for reasons other than name confusion. Post-marketing experience has demonstrated that proprietary names (or components of the proprietary name) can be a source of error in a variety of ways. Consequently, DMEPA considers and evaluates these broader safety implications of the name throughout this assessment and the medication error staff provides additional comments related to the safety of the proposed proprietary name or product based on professional experience with medication errors.

1. Database and Information Sources

DMEPA staff conducts searches of the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to the proposed proprietary name using the criteria outlined in Section 2.1. Section 6 provides a standard description of the databases used in the searches. To complement the process, the DMEPA staff use a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, the DMEPA staff review the USAN stem list to determine if any USAN stems are present within the

proprietary name. The individual findings of multiple safety evaluators are pooled and presented to the CDER Expert Panel.

2. CDER Expert Panel Discussion

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

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

3. FDA Prescription Analysis Studies

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

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, inpatient medication orders and/or outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These orders are optically scanned and one prescription is delivered to a random sample of the 123 participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail. The voice mail messages are then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants send their interpretations of the orders via e-mail to DMEPA.

4. Comments from the OND Review Division

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

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

5. External Proprietary Name Risk Assessment

DMEPA conducts an independent analysis and evaluation of the data provided, and responds to the overall findings of the assessment. When the external proprietary name risk assessment identifies potentially confusing names that were not captured in DMEPA's database searches or in the Expert Panel Discussion, these names are included in the Safety Evaluator's risk assessment and analyzed independently by the Safety

Evaluator to determine if the potentially confusing name could lead to medication errors in usual practice settings.

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

6. Safety Evaluator Risk Assessment of the Proposed Proprietary Name

The primary Safety Evaluator applies his/her individual expertise gained from evaluating medication errors reported to FDA, conducts a Failure Mode and Effects Analysis, and provides an overall risk assessment of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.[8] When applying FMEA to assess the risk of a proposed proprietary name, DMEPA seeks to evaluate the potential for a proposed proprietary name to be confused with another drug name because of name confusion and, thereby, cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to orthographically or phonetically similar drug names prior to approval, where actions to overcome these issues are easier and more effective than remedies available in the post-approval phase.

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

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, Expert Panel Discussion, and prescription studies, external studies, and identifies potential failure modes by asking:

> ***"Is the proposed proprietary name convincingly similar to another drug name, which may cause practitioners to become confused at any point in the usual practice setting?"***

An affirmative answer indicates a failure mode and represents a potential for the proposed proprietary name to be confused with another proprietary or established drug name because of look- or sound-alike similarity. If the answer to the question is no, the Safety Evaluator is not convinced that the names posses 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

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

the name similarity could ultimately cause medication errors in the usual practice setting, the Safety Evaluator will then recommend the use of an alternate proprietary name.

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

a. DDMAC finds the proposed proprietary name misleading from a promotional perspective, and the Review Division concurs with DDMAC's findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a PROPRIETARY name or otherwise [21 U.S.C 321(n); See also 21 U.S.C. 352(a) & (n)].

b. DMEPA identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].

c. FMEA identifies the potential for confusion between the proposed proprietary name and other proprietary or established drug name(s), and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.

d. The proposed proprietary name contains an USAN (United States Adopted Names) stem.

e. DMEPA identifies a potential source of medication error within the proposed proprietary name. For example, the proprietary name may be misleading or, inadvertently, introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug product.

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

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

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

Furthermore, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to rectify post-approval. Educational and other post-approval efforts are low-leverage strategies that have had limited effectiveness at alleviating medication errors involving drug name confusion. Sponsors have undertaken higher-leverage strategies, such as drug name changes, in the past but at great financial cost to the Sponsor and at the expense of the public welfare, not to mention the Agency's

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

Appendix B: FDA Prescription Study Responses (conducted September 14, 2009).

Written Outpatient	Written Inpatient	Verbal Prescription
Zortress	Zortress	Zortres
Zortress	Zortress	Zorta
Zortress	Zortress	Sortras
Zortress	Zortress	Zordtrus
Zartress	Zortress	Zortres
Zortress	Zortress	Zortress
	Zortress	Zortress
	Zostress	
	Zortress	

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

Name	Similarity to Zortress
Clorpres	Look
Nortrel	Look
Ocupress	Look
Zerit	Look
Zestril	Look
Zofran	Look
Zorbitive	Look
Zorbtive	Look
Zotex	Sound

Appendix D: Proprietary names that is internationally registered

Proprietary Name	Similarity to Zortress	Country
Zortrix	Look	Brazil

Appendix E: Product marketed under a different proprietary name

Proprietary Name	Similarity to Zortress	Reason for Discard
(b) (4)	(b) (4)	(b) (4)

Appendix F: Discontinued products with no generic equivalent products available

Proprietary Name	Similarity to Zortress	Month/Year Discontinued
Solotuss (Carbetapentane Tannate)	Look	February 2009

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

Product name with potential for confusion	Similarity to Zortress	Dosage Form/ Strength	Usual Recommended Dose
Zortress **(Everolimus)**	**N/A**	**Tablet: 0.25 mg, 0.5 mg, 0.75 mg, 1 mg**	**0.75 mg twice daily orally**
Fentuss (Guaifenesin/ Hydrocodone) **Discontinued*	Look	Oral syrup: 100 mg/5 mg per 5 mL	Information not available for Fentuss. Similar product: 1 teaspoonful (5 mL) every 4 to 6 hours
Isentress (Raltegravir Potassium)	Look and Sound	Tablet: 400 mg	400 mg twice daily; With rifampin: 800 mg twice daily
Lantus (Insulin Glargine Recombinant)	Look	Injectable: 100 units/mL (10 mL vial, 3 mL cartridge, 3 mL pen)	Various units administered once daily
Lortab (Hydrocodone/ Acetaminophen)	Look	Tablet: 5 mg/500 mg, 10 mg/500 mg	1 to 2 tablet every 4 to 6 hours

Appendix H: Products with numerical similar strength with differentiating product characteristics

Product name with potential for confusion	Similarity to Zortress	Strength	Usual Dose (if applicable)	Differentiating Product Characteristics
Zortress (Everolimus)	**N/A**	**Tablet: 0.25 mg, 0.5 mg, 0.75 mg, 1 mg**	**0.75 mg twice daily orally**	
Lactrase (Lactase) **Over-the-counter*	Look	Capsule: 250 mg	1 to 2 capsule with food	frequency of administration, availability (Lactrase is an over-the-counter product), patient population
Lortuss DM (Brompheniramine/ Dextromethorphan/ Phenylephrine) **Discontinued*	Look	Oral solution: 2 mg/15 mg/7.5 mg per 5 mL	Information not available for Lortuss DM. Similar product dose: 10 mL every 4 to 6 hours	frequency of administration, dosage form, Lortuss DM requires modifier on prescription to distinguish from other Lortuss products, availability (Lortuss DM is discontinued)
Lortuss HC (Hydrocodone/ Phenylephrine) **Discontinued in May 2009*	Look	Oral solution: 3.75 mg/7.5 mg per 5 mL	Information not available for Lortuss HC. Similar product dose: 10 mL every 4 to 6 hours	frequency of administration, dosage form, Lortuss HC requires modifier on prescription to distinguish from other Lortuss products, availability (Lortuss DM is discontinued)
Motrin (Ibuprofen) ** Over-the-counter; Identified* (b) (4)	Look	Tablet: 50 mg, 100 mg, 200 mg Oral suspension: 100 mg/5 mL Oral drops: 40 mg/mL	1 to 2 tablet every 4 to 6 hours.	frequency of administration, availability (Motrin is an over-the-counter product), strength
Zartan (Cephalexin Monohydrate)	Look	Capsule: 500 mg	1 g to 2 g in divided doses every 6 hours, every 8 hours or every 12 hours	dose, unavailability of Zartan, unavailable information on Zartan on commonly used drug references, patient population

Appendix I: Potential confusing name with overlap in prescribing directions

Zortress **(Everolimus)**	**Strength:** **Tablet: 0.25 mg, 0.5 mg, 0.75 mg, 1 mg**	**Dose: 0.75 mg twice daily orally**
Failure Mode: Name confusion	**Causes**	**Effects**
(b) (4)	(b) (4)	(b) (4)
Zostrix 0.025% (Capsaicin) Cream Zostrix HP 0.075% (Capsaicin) Cream Zostrix Neuropathy 0.25% (Capsaicin) Cream **Over-the-counter*	Orthographic similarities: Both names start with 'Zo-' and 'Zortre-' and 'Zostri-' are very similar. Numerically similar strengths: 0.25 mg vs. 0.25% or 0.025%; 0.75 mg vs. 0.075%.	The differences in product characteristic differences minimize the likelihood of medication errors in usual practice settings. *Rationale:* Although there are some orthographic similarities and both products can be ordered inpatient, the difference in product characteristics such as dosage form (tablet vs. cream), route of administration (oral vs. topical), strength unit (mg vs %) and frequency of administration (twice daily vs. three to four times daily) minimize the risk of confusion between the two products. Additionally, although there are numerical similarities in the strengths of both products, it is unlikely that Zostrix will be prescribed using the strength of the product as they are marketed as Zostrix (regular strength), Zostrix HP (high potency) and Zostrix Neuropathy Cream, which correspond to the 0.025%, 0.075% and 0.25% strengths, respectively.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21560	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	CERTICAN (EVEROLIMUS) TABLETS

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

/s/

JUDY J PARK
01/11/2010

CARLOS M MENA-GRILLASCA
01/11/2010

DENISE P TOYER
01/11/2010

DENISE P TOYER on behalf of KELLIE A TAYLOR
01/11/2010

CAROL A HOLQUIST
01/11/2010