

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125359Orig1s000

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: November 7, 2011

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Drug Name: Erwinaze (Asparaginase *Erwinia Chrysanthemi*) for
Injection
10,000 International Units per vial

Application Type/Number: BLA 125359

Applicant: EUSA Pharma (USA) Inc.

OSE RCM #: 2011-3511

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1 INTRODUCTION

This review evaluates the proposed proprietary name, Erwinaze, 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

DMEPA found the proposed name, Erwinaze, acceptable in OSE Review 2010-1155/2010-2399, dated November 10, 2010 which evaluated the proprietary name under both the IND and BLA.

Because more than one year has passed since the Prescription Studies were completed for Erwinaze, DMEPA has conducted a full re-review of the name.

1.2 PRODUCT INFORMATION

The Applicant provided the following product information for Erwinaze as part of their May 13, 2010 and November 8, 2010 submissions. The indication of use and dosing regimen reflect current internal revisions to the insert labeling.

- Established Name:
(Asparaginase *Erwinia Chrysanthemi*), recently assigned
- Indication of Use:
Erwinaze is indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of [REDACTED] ^{(b) (4)} patients with acute lymphoblastic leukemia (ALL) [REDACTED] ^{(b) (4)} who have developed hypersensitivity to *E. coli*-derived asparaginase
- Route of administration:
Intramuscular
- Dosage form:
for Injection
- Dose:
To substitute for a dose of pegaspargase: 25,000 International Units/m² intramuscularly three times a week (Monday/Wednesday/Friday) for six doses for each planned dose of pegaspargase
To substitute for a dose of native E. coli asparaginase: 25,000 International Units/m² intramuscularly for each scheduled dose of native *E. coli* asparaginase within a treatment
- How Supplied:
Cartons containing 5 vials
- Storage:
Refrigeration 2°C to 8°C (36°F to 46°F). Protect from light.

Additionally, Erwinaze is an orphan drug and is approved in some foreign countries under the name, Erwinase.

2 RESULTS

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

2.1 PROMOTIONAL ASSESSMENT

DDMAC determined the proposed name is acceptable from a promotional perspective. DMEPA and the Division of Biologic Oncology Products concurred with the findings of DDMAC's promotional assessment of the proposed name.

2.2 SAFETY ASSESSMENT

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

2.2.1 *United States Adopted Names (USAN) SEARCH*

The October 12, 2011 United States Adopted Name (USAN) stem search, identified that a USAN stem is not present in the proposed proprietary name.

2.2.2 *Components of the Proposed Proprietary Name*

This proposed proprietary name, Erwinaze, is comprised of a single word. However, the beginning five letters ("Erwin") comprising the name are derived from "Erwinia", the proper name. Although this overlap exists, "Erwinia" is the second component of the three component proper name (*Asparaginase Erwinia Chrysanthemi*) which helps to decrease the likelihood for confusion between the proposed name and the proper name. Also, see Section 2.2.3, below, for the results of our postmarketing search on the product.

2.2.3 *FDA Adverse Event Reporting System (AERS) Selection of Cases*

The name, Erwinase, [REDACTED] (b) (4) [REDACTED] has been used for this product for at least 20 years and is approved in some foreign countries. Due to the fact that the proposed name Erwinaze differs from Erwinase by only one letter in the seventh position ("z" vs. "s") and the names sound identical, the FDA Adverse Event Reporting System (AERS) was searched for medication errors involving Erwinase. An AERS search was conducted in our previous review of Erwinaze in OSE Review 2010-1155/2010-2399. Therefore, for this review, an updated search was conducted to cover the dates since our previous search. The updated search was conducted on October 16, 2011 and was limited to the dates September 10, 2010 through October 16, 2011. The AERS database was searched using the verbatim term "Erw%" and MedDRA High Level Group Terms (HGLTs) "Medication Errors" and "Product Quality Issues".

The reports were manually reviewed to determine if a medication error occurred. Duplicate reports were combined into cases. Cases that described a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors. If the root cause(s) were associated with name confusion involving Erwinase, the cases were considered pertinent to this review. Those cases that did not describe a medication error or did not describe an error applicable to this review were excluded from further analysis.

The search yielded one case (ISR #7150234) which described a wrong drug error that occurred in a clinical study and adverse drug reactions that occurred after the patient was “switched to Erwinia”. Erwinase was listed as one of the “suspect products” in the case so it appears the reporter was using the name Erwinia instead of the name Erwinase. Based on this one case, it is difficult to determine how often Erwinase is referred to as “Erwinia”. However, we note the proper name for this product is now Asparaginase *Erwinia Chrysanthemi* rather than the previous *Erwinia* L-asparaginase which may impact how the proper name is used since *Erwinia* is now in the middle portion of the proper name rather than in the beginning.

2.2.4 FDA Name Simulation Studies

Thirty-five practitioners participated in DMEPA’s prescription studies. In the Written Inpatient Study all practitioners interpreted the letter “z” as either the letter “r” or “s”. All respondents in the Verbal Prescription Study interpreted the letter “z” as the letter “s” and six of the practitioners in the same study interpreted the beginning letter “E” as the letter “I”. We did not identify any names in the prescription studies that overlap with a currently marketed product. See Appendix C for the complete listing of interpretations from the verbal and written prescription studies.

We note the word “international” was inadvertently omitted from the strength in the Written Outpatient Study and the Verbal Prescription Study. However, the word “units” was written/stated; thus, we believe the omission had no impact on the study results.

2.2.5 Comments from Other Review Disciplines

In our initial review of the name, Erwinaze, the Division of Biologic Oncology Products did not forward any comments or concerns relating to the proposed name at the initial phase of the review.

2.2.6 Failure Mode and Effects Analysis of Similar Names

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

Table 1: Collective List of Potentially Similar Names (DMEPA, EPD, Other Disciplines, and External Name Study if applicable)

Look Similar		Sound Similar		Look and Sound Similar	
Name	Source	Name	Source	Name	Source
Enemeez	EPD Panel	Eryzole	EPD Panel	(b) (4)	EPD Panel
Erwinia Asparaginase	EPD Panel	Patanase	EPD Panel	(b) (4)	EPD Panel
(b) (4)	EPD Panel	Agenerase	EPD Panel	Allernaze	EPD Panel

Look Similar		Sound Similar		Look and Sound Similar	
Name	Source	Name	Source	Name	Source
Ertaczo	EPD Panel			Invirase	EPD Panel
Solaraze	EPD Panel			Aerinaze	EPD Panel
Aranesp	EPD Panel			Pancreaze	EPD Panel
Invanz	EPD Panel			(b) (4)	EPD Panel
Sublimaze	EPD Panel			Orinase	EPD Panel
Brevinaze	EPD Panel			Estrace	EPD Panel
E-mycin	EPD Panel			Ceredase	EPD Panel
Efavirenz	EPD Panel				
Avinza	EPD Panel				
(b) (4)	EPD Panel				
Enulose	EPD Panel				
Crixivan	EPD Panel				
Evoclin	EPD Panel				
Eraxis	EPD Panel				
Eskalith	EPD Panel				
Essian	EPD Panel				
Oncaspar	EPD Panel				
Crinone	EPD Panel				

Our analysis of the 34 names contained in Table 1 considered the information obtained in the previous sections along with the product characteristics. We determined the 34 names will not pose a risk for confusion as described in Appendices D and E.

2.2.6 Communication of DMEPA's Final Decision to Other Disciplines

DMEPA communicated the findings from our previous review of Erwinaze to DBOP via e-mail on September 23, 2010. At that time we also requested additional information or concerns that could inform our review. Per e-mail correspondence from DBOP on September 23, 2010, they stated no additional concerns with the proposed proprietary name, Erwinaze.

3 CONCLUSIONS

The re-evaluation of the proposed proprietary name, Erwinaze, did not identify any vulnerabilities that would result in medication errors with the additional names noted in

this review. Thus, DMEPA has no objection to the proprietary name, Erwinaze, for this product at this time.

DMEPA considers this a final review; however, if approval of the BLA is delayed beyond 90 days from the date of this review, the Division of Biologic Oncology Products should notify DMEPA because the proprietary name must be re-reviewed prior to the new approval date. If you have further questions or need clarifications, please contact Sue Kang, OSE project manager, at 301-796-4216.

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.

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. *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.

13. *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.

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 promotional and safety aspects of a proposed proprietary name. The promotional review of the proposed name is conducted by DDMAC. DDMAC 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. DDMAC 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

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

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. 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 product characteristics considered for this review appears in Appendix B1 of this review.

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).

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
	Similar spelling	Identical prefix	• Names may appear similar

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

Look-alike		Identical infix Identical suffix Length of the name Overlapping product characteristics	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 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 Division of Drug Marketing, Advertising, and Communications (DDMAC). 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 DDMAC'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 characteristics listed in Appendix B1 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

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

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. 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 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 with Possible Orthographic or Phonetic Misinterpretation

Letters in Name Erwinaze	Scripted May Appear as	Spoken May Be Interpreted as
Capital 'E'	Capital 'F', 'C'	Any vowel
Lower case 'r'	'n', 's', 'v', 'u', 'x', or 't'	
Lower case 'w'	'v', 'u', or 'm'	'v'
Lower case 'i'	'e' or 'l'	Any vowel
Lower case 'n'	'm', 'u', 'x', 'r', 'h', or 's'	
Lower case 'a'	'c', 'o', or 'u'	Any vowel
Lower case 'z'	'c', 'l', 'm', 'n', 'r', 's', 't', and 'x'	's'
Lower case 'e'	'i', 'l', or 'o'	Any vowel
'Er'		'Ir' or 'Ur'
'win'		'when' or 'wen'

Appendix C: Prescription Simulation Samples and Results

Figure 1. Erwinaze Study (Conducted on September 30, 2011)

Handwritten Requisition Medication Order	Verbal Prescription
<p>Medication Order:</p> <p><i>Erwinaze 20,000 International Units IM on Mar</i></p> <p>Outpatient Prescription:</p> <p><i>Erwinaze 10,000 unit per vial Bring to clinic Day # 2</i></p>	<p>Erwinaze 10,000 unit vial Dispense 2 vials to bring to clinic</p>

FDA Prescription Simulation Responses

Inpatient Medication Order	Outpatient Prescription	Voice Prescription
CRURUARE	EREVEZE	ARINASE
CRURUARE	ERIVENEZE	ERWANESE
ELURUASE	ERIVENEZE	ERWINASE
ENORVARE	ERUMEZE	ERWINASE
ENVINARE	ERUVENEZE	ERWINASE
ENVIRASE	ERWENEZE	IRWINASE
ENWASE	ERWENEZE	IRWINASE
ERURNASE	ERWENYE	IRWINASE
ERURVASE	ERWINEYE	IRWINASE
ERVRUARE		IRWINASE
ERWINARE		IRWINASE
ERWINARE		
ERWINASE		
ERWINASE		

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

	Proprietary Name	Similarity to Erwinaze	Failure preventions
1	Erwinia Asparaginase	Look	<i>Erwinia</i> L-Asparaginase (b) (4) The proper name has been changed to Asparaginase <i>Erwinia Chrysanthemi</i> .
2	Ertaczo (Spectazole Nitrate)	Look	Name lacks convincing orthographic or phonetic similarity to Erwinaze
3	Sublimaze (Fentanyl)	Look	Name lacks convincing orthographic or phonetic similarity to Erwinaze
4	E-mycin (Erythromycin)	Look	Name lacks convincing orthographic or phonetic similarity to Erwinaze
5	Avinza (Morphine Sulfate)	Look	Name lacks convincing orthographic or phonetic similarity to Erwinaze
6	(b) (4)		
7	Crixivan (Indinavir)	Look	Name lacks convincing orthographic or phonetic similarity to Erwinaze
8	Evoclin (Clindamycin)	Look	Name lacks convincing orthographic or phonetic similarity to Erwinaze
9	Eskalith (Lithium Carbonate)	Look	Name lacks convincing orthographic or phonetic similarity to Erwinaze
10	Essian (Esterified Estrogens and Methyltestosterone)	Look	Name lacks convincing orthographic or phonetic similarity to Erwinaze
11	Oncaspar (Pegaspargase)	Look	Name lacks convincing orthographic or phonetic similarity to Erwinaze
12	Eryzole (Erythromycin Ethylsuccinate and Sulfisoxazole)	Sound	Name lacks convincing orthographic or phonetic similarity to Erwinaze
13	(b) (4)		
14	Patanase (Olapatadine)	Sound	Name lacks convincing orthographic or phonetic similarity to Erwinaze
15	Agenerase (Amprenavir)	Sound	Name lacks convincing orthographic or phonetic similarity to Erwinaze

	Proprietary Name	Similarity to Erwinaze	Failure preventions
16	Estrace (Estradiol)	Look and Sound	Name lacks convincing orthographic or phonetic similarity to Erwinaze
17	Brevinaze (Ketamine)	Look	Foreign name (South Africa)
18	Aerinaze (Desloratidine and Pseudoephedrine)	Look and Sound	Foreign name (Europe)
19	Enulose (Lactulose)	Look	This name was evaluated in our previous review of Erwinaze (OSE Review 2010-1155/2010-2399) and did not pose a safety concern
20	Aranesp (Darbepoetin Alfa)	Look	This name was evaluated in our previous review of Erwinaze (OSE Review 2010-1155/2010-2399) and did not pose a safety concern
21	Allernaze (Triamcinolone Acetonide, USP)	Look and Sound	This name was evaluated in our previous review of Erwinaze (OSE Review 2010-1155/2010-2399) and did not pose a safety concern.
22	(b) (4)		
23	Invirase (Saquinavir)	Look and Sound	This name was evaluated in our previous review of Erwinaze (OSE Review 2010-1155/2010-2399) and did not pose a safety concern.
24	Orinase (Tolbutamide)	Look and Sound	This name was evaluated in our previous review of Erwinaze (OSE Review 2010-1155/2010-2399) and did not pose a safety concern.
25	Ceredase (Alglucerase)	Look and Sound	This name was evaluated in our previous review of Erwinaze (OSE Review 2010-1155/2010-2399) and did not pose a safety concern.

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: Erwinaze (Asparaginase Enzyme) (Chrysomil brand)	Strength: 10,000 International Units per vial	Usual dose: To substitute for a dose of neosarazine, 25,000 International Units/m ² intramuscularly three times a week (Monday/Wednesday/Friday) for six doses for each planned dose of neosarazine. To substitute for a dose of native E. coli asparaginase, 25,000 International Units/m ² intramuscularly for each scheduled dose of native E. coli asparaginase within a treatment.
	Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion	Causes (could be multiple)	Prevention of Failure Mode
26	(b) (4)		
27	<p>Invanz (Ertapenem) for Injection</p> <p><u>Strength:</u> 1 g per vial</p> <p><u>Dosage:</u> 1 gm intravenously or intramuscularly once daily</p>	<p><u>Orthographic:</u> The beginning letters “Er” vs. “In” may look similar when scripted. Both names contain the letter “z”.</p> <p><u>Route of administration:</u> Both products can be administered intramuscularly</p>	<p><u>Orthographic:</u> Erwinaze appears longer in length when scripted. The letter “n” in Erwinaze is followed by three letters whereas the letter “n” in Invanz is followed only by the letter “z” which helps to differentiate the names.</p> <p><u>Dose:</u> 25,000 International Units/m² vs. 1 g (1,000 mg)</p>

	Proposed Name Erwinaze (Asparaginase <i>Erwinaze</i> <i>Chrysothamn</i>)	Strength 10,000 International Units per mL	Usual Dose To substitute for a dose of pegaspargase 25,000 International Units/m ² intramuscularly three times a week (Monday/Wednesday/Friday) for six doses for each planned dose of pegaspargase To substitute for a dose of native <i>E. coli</i> asparaginase 25,000 International Units/m ² intramuscularly for each scheduled dose of native <i>E. coli</i> asparaginase within a treatment
	Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion	Causes (could be multiple)	Prevention of Failure Mode
28	<p>Crinone (Progesterone) Gel</p> <p><u>Strength:</u> 4% and 8%</p> <p><u>Dosage:</u> 1 applicatorful vaginally once daily, twice daily, or every other day</p>	<p><u>Orthographic:</u> The beginning letters “E” vs. “C” may look similar when scripted. The letters “ina” look similar to the letters “ino”.</p>	<p><u>Orthographic:</u> The letter “w” and the downstroke letter “z” in Erwinaze help to differentiate the names.</p> <p><u>Dose:</u> 25,000 International Units/m² vs. 1 applicatorful</p>

	Proposed name: Erwinaze (Asparaginase <i>Erwinia</i> <i>Chrysanthemum</i>)	Strength: 10,000 International Units per vial	Usual dose: To substitute for a dose of pegaspargase, 25,000 International Units/m ² intramuscularly three times a week (Monday/Wednesday/Friday) for six doses for each planned dose of pegaspargase. To substitute for a dose of native E. coli asparaginase, 25,000 International Units/m ² intramuscularly for each scheduled dose of native <i>E. coli</i> asparaginase within a treatment.
	Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion	Causes (could be multiple)	Prevention of Failure Mode
29	<p>Pancreaze (Pancrease) Delayed-release Capsules (contains Lipase, Protease and Amylase)</p> <p><u>Strength:</u> 4,200/10,000/17,500 units 10,000/25,000/43,750 units 16,800/40,000/70,000 units 21,000/37,000/61,000 units</p> <p><u>Dosage:</u> 500 to 1,000 lipase units/kg of body weight per meal to a maximum of 2,500 lipase units/kg of body weight per meal (or less than or equal to 10,000 lipase units/kg of body weight per day), or less than 4,000 lipase units/g fat ingested per day</p>	<p><u>Orthographic:</u> The beginning letters “E” vs. “P” may look similar when scripted. Both names end with the letters “aze”.</p> <p><u>Dose:</u> The Pancreaze dose is based on Lipase units which could overlap with the dose of Erwinaze (e.g., 21,000 lipase units vs. 21,000 International Units)</p>	<p><u>Context of use:</u> Erwinaze is a chemotherapeutic agent and would likely be a part of a set of orders identified as “Chemotherapy” on an order sheet. Additionally, an order for Erwinaze would typically state the mg/m² dose to be administered as well as the calculated dose which would help to differentiate it from Pancreaze. This is one of a number of recommendations from the American Society of Health-System Pharmacists for the preventing medication errors with antineoplastic agents.⁴ Furthermore, Erwinaze should be administered in a setting where resuscitation equipment and other agents necessary to treat anaphylaxis are available. Therefore, a patient would not be given a prescription for Erwinaze whereas a prescription would be given to a patient for Pancreaze which can be self-administered and used in the home setting.</p>

⁴ American Society of Health-System Pharmacists. ASHP guidelines on preventing medication errors with antineoplastic agents. *Am J Health-Syst Pharm.* 2002; 59:1648–68.

	Proposed name Erwinaze (Asparaginase Erwinaze (E. coli) suspension)	Strength 10,000 International Units per vial	Usual dose To substitute for a dose of pegaspargase: 25,000 International Units/m ² intravenously three times a week (Monday/Wednesday/Friday) for six doses for each planned dose of pegaspargase. To substitute for a dose of native E. coli asparaginase: 25,000 International Units/m ² intramuscularly for each scheduled dose of native E. coli asparaginase within a treatment.
	Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion	Causes (could be multiple)	Prevention of Failure Mode
30	Enemeez (Docusate Sodium) Rectal Enema <u>Strength:</u> 283 mg <u>Dosage:</u> One enema as needed	<u>Orthographic:</u> Both names begin with the letter "E" and contain the downstroke letter "z" in the seventh position.	<u>Dose:</u> 25,000 International Units/m ² vs. 1 applicatorful
31	Solaraze (Diclofenac Sodium) Gel <u>Strength:</u> 3% <u>Dosage:</u> Apply enough gel to cover each lesion. Normally, 0.5 g of gel is used on each 5 cm x 5 cm lesion site	<u>Orthographic:</u> Both names contain eight letters end with the letters "aze". The fifth position letter "n" in Erwinaze may look similar to the fifth position letter "r" in Solaraze.	<u>Orthographic:</u> The beginning letters "E" vs. "S" do not look similar. Solaraze contains the upstroke letter "l" whereas Erwinaze does not contain any upstroke letters. <u>Dose:</u> 25,000 International Units/m ² vs. 1 application

	Proposed name Erwinaze (Asparaginase <i>Erwinaze</i> (Chapsakleam))	Strength 10,000 International Units orally	Usual dose To substitute for a dose of pegaspargase: 25,000 International Units/m ² intramuscularly three times a week (Monday/Wednesday/Friday) for six doses for each planned dose of pegaspargase. To substitute for a dose of native E. coli asparaginase: 25,000 International Units/m ² intramuscularly for each scheduled dose of native <i>E. coli</i> asparaginase within a treatment.
	Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion	Causes (could be multiple)	Prevention of Failure Mode
32	<p>Efavirenz (Established name for Sustiva) Capsules and Tablets</p> <p><u>Strength:</u> <i>Capsules</i> 50 mg and 200 mg <i>Tablets</i> 600 mg</p> <p><u>Dosage:</u> <i>Adults</i> 600 mg once daily <i>Children</i> 200 mg to 600 mg orally once daily based on weight</p>	<p><u>Orthographic:</u> Both names begin with the letter “E”, contain the letter “i” in the infix of the name, and the letter “z” at the end.</p>	<p><u>Orthographic:</u> Efavirenz contains the upstroke letter “f” whereas Erwinaze does not contain any upstroke letters.</p> <p><u>Dose:</u> 25,000 International Units/m² vs. 200 mg to 600 mg once daily</p>

	Proposed Name: Trialyte <i>(Asparaginase E. coli)</i> <i>(Ch. xochitl/ml)</i>	Strength: 10,000 International Units per vial	Usual Dose: To substitute for a dose of neosarase, 25,000 International Units/ml intramuscularly three times a week (Monday/Wednesday/Friday) for six doses for each planned dose of neosarase. To substitute for a dose of native E. coli asparaginase, 25,000 International Units/ml intramuscularly for each scheduled dose of native E. coli asparaginase within a treatment.
	Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion	Causes (could be multiple)	Prevention of Failure Mode
33	(b) (4)		

	Proposed name: Erwinaze (Asparaginase/Erwinin Chrysalidase)	Strength: 10,000 International Units per vial	Usual dose: To substitute for a dose of native asparaginase: 25,000 International Units/m ² intravenously three times a week (Monday/Wednesday/Friday) for six doses for each planned dose of native asparaginase. To substitute for a dose of native <i>E. coli</i> asparaginase: 25,000 International Units/m ² intravenously for each scheduled dose of native <i>E. coli</i> asparaginase within a treatment.
	Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion	Causes (could be multiple)	Prevention of Failure Mode
34	<p>Eraxis (Anidulafungin) for Injection</p> <p><u>Strength:</u> 50 mg per vial and 100 mg per vial</p> <p><u>Dosage:</u> Loading dose: 200 mg intravenously once on Day 1, followed by 100 mg intravenously once daily</p> <p>Loading dose: 100 mg intravenously once on Day 1, followed by 50 mg intravenously once daily</p>	<p><u>Orthographic:</u> Both names begin with the letters "Er".</p>	<p><u>Orthographic:</u> Erwinaze appears longer in length when written. Eraxis contains the cross-stroke letter "x" whereas Erwinaze does not.</p> <p><u>Dose:</u> 25,000 International Units/m² vs. 200 mg or 100 mg once on Day 1, followed by 50 mg or 100 mg once daily</p>

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: November 10, 2010

Application IND 000290

Type/Number: BLA 125359

Through: Kristina A. Toliver, PharmD, Team Leader *Kristina A. Toliver 11/10/2010*
Denise P. Toyer, PharmD, Deputy Director *Denise P. Toyer 11/10/2010*
Division of Medication Error Prevention and Analysis (DMEPA)

From: Loretta Holmes, BSN, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis (DMEPA) *Loretta Holmes 11/15/10*

Subject: Proprietary Name Review

Drug Name: Erwinaze (*Erwinia* L-asparaginase) for Injection
10,000 International Units per vial

Sponsor: EUSA Pharma (USA) Inc.

OSE RCM #: 2010-1155/2010-2399

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

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EXECUTIVE SUMMARY

This review summarizes DMEPA's proprietary name risk assessment of Erwinaze (*Erwinia* L-asparaginase) for Injection, 10,000 International Units per vial. Our evaluation did not identify concerns that would render the name unacceptable based on the product characteristics and safety profile known at the time of this review. Thus, DMEPA finds the proposed proprietary name, Erwinaze, acceptable for this product. The proposed proprietary name must be re-reviewed 90 days before approval of the BLA.

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 responds to May 13, 2010 and November 8, 2010 requests from EUSA Pharma (USA), Inc. for an assessment of the proposed proprietary name, Erwinaze, regarding potential name confusion with other proprietary or established drug names in the usual practice settings.

1.2 REGULATORY HISTORY

(b) (4)

1.3 PRODUCT INFORMATION

Erwinaze contains the purified enzyme L-asparagine amidohydrolase (L-asparaginase) derived in (b) (4) from from the non-human (plant) pathogen *Erwinia chrysanthemi*. Erwinaze is indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with acute lymphoblastic leukemia and hypersensitivity to (b) (4). The recommended dose is 25,000 International Units/m² injected intramuscularly three times a week for two weeks for every course of asparaginase treatment. (b) (4)

(b) (4) Erwinaze will be supplied as a lyophilisate that must be reconstituted with 1 mL to 2 mL of 0.9% sodium chloride before use. Each vial will contain 10,000 International Units. The vial should be stored at 2-8°C (36-46°F). The solution should be administered within 15 minutes of reconstitution. (b) (4)

(b) (4)

2 METHODS AND MATERIALS

Appendix A describes the general methods and materials used by the Division of Medication Error Prevention and Analysis (DMEPA) when conducting a proprietary name risk assessment for all proprietary names. Sections 2.1, 2.2 and 2.3 identify specific information associated with the methodology for the proposed proprietary name, Erwinaze.

2.1 SEARCH CRITERIA

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

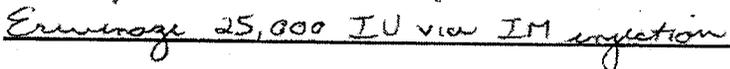
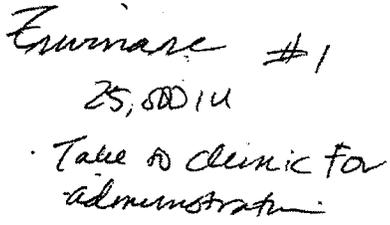
To identify drug names that may look similar to Erwinaze, the DMEPA Safety Evaluators also consider the orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (eight letters), upstrokes (none), downstrokes (one, lower case ‘z’), cross strokes (two, capital letter ‘E’ and lower case ‘z’ when written with a crossbar), and dotted letters (one, lower case ‘i’). Additionally, several letters in Erwinaze may be vulnerable to ambiguity when scripted (see Appendix B). As a result, the DMEPA Safety Evaluators also considers these alternate appearances when identifying drug names that may look similar to Erwinaze.

When searching to identify potential names that may sound similar to Erwinaze, the DMEPA Safety Evaluators search for names with similar number of syllables (three), stresses (ER-win-aze, er-WIN-aze, or er-win-AZE), and placement of vowel and consonant sounds. Additionally, the DMEPA Safety Evaluators consider that pronunciation of parts of the name can vary (see Appendix B). The Sponsor’s intended pronunciation of the name is “ER-win-aze”. However, names are often mispronounced and/or spoken with regional accents and dialects, so other potential pronunciations of the name are considered.

2.2 FDA PRESCRIPTION ANALYSIS STUDIES

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

Figure 1. Erwinaze Prescription Studies (conducted on June 18, 2010)

HANDWRITTEN REQUISITION MEDICATION ORDER	VERBAL PRESCRIPTION
<p><u>Inpatient Medication Order:</u> </p>	<p>“Erwinaze #1 25,000 IU Take to clinic for administration”</p>
<p><u>Outpatient Prescription:</u> </p>	

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

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

2.3 EXTERNAL PROPRIETARY NAME RISK ASSESSMENT

For this product, the Sponsor submitted an external evaluation of the proposed proprietary name. The Division of Medication Error Prevention and Analysis 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 associated with the proposed name, the Safety Evaluator compares the findings of their overall risk assessment with the findings of the proprietary name risk assessment submitted by the Sponsor. The Safety Evaluator then determines whether the Division's risk assessment concurs or differs with the findings. When the proprietary name risk assessments differ, the Division of Medication Error Prevention and Analysis provides a detailed explanation of these differences.

2.4 ADVERSE EVENTS REPORTING SYSTEM (AERS) SEARCH

The Sponsor indicated the (b) (4) name, Erwinase, has been used for this product for at least 20 years and the name is approved in some foreign countries. Due to the fact that the proposed name, Erwinaze, differs from Erwinase by only one letter in the seventh position ("z" vs. "s") and the names sound identical, this Safety Evaluator searched the FDA Adverse Event Reporting System (AERS) for medication errors involving Erwinase. DMEPA previously conducted an AERS search for medication errors involving Erwinase in OSE Review 2009-2116. Therefore, for this review, an updated search was conducted to cover the dates since our previous search. The updated search was conducted on September 9, 2010 and was limited to the dates January 1, 2010 through September 9, 2010. The AERS database was searched using the verbatim term "Erw%" and the MedDRA High Level Group Terms (HLGTs) "Medication Errors" and "Product Quality Issues".

3 RESULTS

3.1 DATABASE AND INFORMATION SOURCES

The DMEPA searches yielded a total of seven names as having some similarity to the name Erwinaze.

Six of the seven names were thought to look like Erwinaze. These include Amerge, Unicare, Aranesp, Brevinaze, Enoxacin, and Ertaczo. The remaining name, Erwinase (Crisantapase) was thought to look and sound similar to Erwinaze.

Additionally, DMEPA Safety Evaluators did not identify any United States Adopted Names (USAN) stems in the proposed proprietary name as of September 10, 2010.

3.2 CDER EXPERT PANEL DISCUSSION

The Expert Panel reviewed the pool of names identified by DMEPA Safety Evaluators (see Section 3.1 above) and noted no additional names were thought to have orthographic or phonetic similarity to Erwinaze.

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 42 practitioners responded. Four of the practitioners interpreted the name correctly as "Erwinaze". The remainder of the practitioners misinterpreted the drug name. None of the responses overlapped with any

existing or proposed drug names in the United States. In the outpatient and verbal studies, all responses were misspelled orthographic or phonetic variations, respectively, of the proposed name, Erwinaze. We note that in the all three studies, there were instances where the letter "z" in Erwinaze was misinterpreted as the letter "s". See Appendix C for the complete listing of interpretations from the verbal and written prescription studies.

3.4 EXTERNAL PROPRIETARY NAME STUDY

In the external proposed proprietary name risk assessment, the Sponsor conducted an independent search of the Drugs@FDA database. The Sponsor identified a total of 10 drug names thought to have some potential for confusion with the name Erwinaze (Amphadase, Arimidex, Arixtra, Aromasin, Avage, Eurax, Retavase, Urese, Wydase, and Enulose). The Sponsor also conducted a search by search engines (no explanation provided), from which no similar names were identified.

These 10 names are identical to the names identified by the Sponsor in their submission for a proprietary name review request for Erwinaze (see OSE Review 2009-2116). None of these 10 names were previously identified in the DMEPA staff searches, the Expert Panel Discussion, or FDA prescription studies. The type of similarity (orthographic, phonetic, or both) was not specified. Therefore, DMEPA included the 10 names in our analysis of the proposed proprietary name for look-alike and sound-alike similarity to Erwinaze. The Sponsor concluded that these 10 names would not cause confusion that could lead to medication errors in the usual practice setting.

3.5 ADVERSE EVENT REPORTING SYSTEM (AERS) SEARCH

This Safety Evaluator's updated search of the Adverse Event Reporting System did not retrieve any cases.

3.6 COMMENTS FROM THE DIVISION OF BIOLOGIC ONCOLOGY PRODUCTS (DBOP)

3.6.1 Initial Phase of Review

In response to the OSE June 2, 2010 e-mail, the Division of Biologic Oncology Products (DBOP) stated "DBOP has no concerns with this name at this time."

3.6.2 Midpoint of Review

On September 23, 2010, DMEPA notified insert review division via e-mail that we had no objections to the proposed proprietary name, Erwinaze. Per e-mail correspondence from DBOP on September 23, 2010, the Division stated they are "fine with "Erwinaze"."

3.7 SAFETY EVALUATOR RISK ASSESSMENT

Independent searches by the primary Safety Evaluator resulted in identification of two additional names, Buminate and Allernaze, which were thought to look similar to Erwinaze and represent a potential source of drug name confusion. Additionally, the names Erwinase and Erwinaze differ by only one letter in the seventh position ("s" vs. "z") and these letters may look similar if the letter "z" is written without a downstroke. Therefore, the names with orthographic and/or phonetic similarity that were identified in our review of Erwinase were re-evaluated for their potential orthographic and/or phonetic similarity to Erwinaze. Those names that overlapped with the names identified in the current EPD panel searches (Section 3.1) and external proprietary name study (Section 3.4) for Erwinaze have been omitted from this list. The following names were evaluated in our review of Erwinase. The names with look-alike similarity are: Arranon, Oraverse, Ceredase, Beconase, Freamine, Cervarix, Carnosine, Cavirinse, Micronase, Invirase, Eraxis, Etreftinate, Irokinase, Orabase, Errin, Evamist, Renese, and Iressa. The name with phonetic similarity is: (b) (4). The names with orthographic and phonetic similarity are: Orinase and Eminase.

Thus, we evaluated a total of 40 names: seven were identified in Database and Information Sources, 10 were identified in the External Name Study, and 23 were identified in this section by the primary Safety Evaluator.

4 DISCUSSION

This proposed name was evaluated from a safety and promotional perspective based on the product characteristics provided by the Sponsor. We sought input from pertinent disciplines involved with the review of this application and considered it accordingly.

4.1 PROMOTIONAL ASSESSMENT

DDMAC evaluated the name, Erwinaze, from a promotional perspective and determined the name was acceptable. The Division of Biologic Oncology Products and the Division of Medication Error Prevention and Analysis concurred with this assessment.

4.2 SAFETY ASSESSMENT

In total, 40 names were identified as potential sources of name confusion with the proposed proprietary name, Erwinaze. DMEPA did not identify other aspects of the name that could function as a source of error. One of the 40 names identified, Erwinase (Crisantapase), is a trademark registered to (b) (4) in the U.S. and several foreign countries and is the subject of this review. Therefore, this name was removed from further analysis. Twenty-one of the remaining 39 names were not evaluated further for the following reasons: 17 names lack orthographic and/or phonetic similarity, two are names of discontinued products, one is a proposed name that was found unacceptable and an alternate name has been approved for the product, and one is a foreign drug product name (see Appendices D through G).

Failure mode and effects analysis (FMEA) was then applied to determine if the proposed name could potentially be confused with the remaining 18 names and lead to medication errors.

This analysis determined that the name similarity between Erwinaze and these 18 products is unlikely to result in medication errors for the reasons presented in Section 4.2.1 and Appendices H through J. This finding is consistent with and supported by an independent risk assessment of the proprietary name submitted by the Sponsor.

4.2.1 Erwinaze and Ceredase

(b) (4). Although the proposed name, Erwinaze, has orthographic similarities and the characteristics of both products remain the same, our analysis has determined that these two products can co-exist in the marketplace.

Data from the May 22, 2008³ Periodic Adverse Experience Report for Ceredase, indicates that only three patients in the United States had exposure to the commercially available product during that time. Additionally, we note that the Medical Officer's Review of Periodic Adverse Experience Report 0401/08 – 03/31/09 dated July 9, 2010 indicates that all but five patients formerly treated with Ceredase have been transitioned to Cerezyme, a recombinant form of β -glucocerebrosidase.

³ Ceredase (Alglucerase Injection), NDA 020057. Periodic Adverse Drug Experience Report, dated May 22, 2008. The period covered in this submission is April 1, 2007 through March 31, 2008.

Additionally, both Ceredase and the proposed product Erwinaze, appear to have been available concurrently in several foreign countries (Germany, Norway, and the United Kingdom). Our search of the AERS database did not identify any medication error cases that involve name confusion between these two products. We recognize that the lack of reports does not imply that no errors have occurred. However, the limited number of patients receiving Ceredase will likely minimize the potential for confusion with the proposed Erwinaze product.

5 CONCLUSIONS AND RECOMMENDATIONS

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

However, if any of the proposed product characteristics as stated in this review are altered prior to approval of the BLA, 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 you have further questions or need clarification, please contact Sue Kang, OSE Project Manager, at 301-796-4216.

5.1 COMMENTS TO THE SPONSOR

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

6 REFERENCES

1. *Adverse Events Reporting System (AERS)*

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

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

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

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

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

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

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

5. *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.

6. *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.

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

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

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

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

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

Provides information regarding patent and trademarks.

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

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

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

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

12. **Natural Medicines Comprehensive Databases** (www.naturaldatabase.com)

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

13. **Stat!Ref** (www.statref.com)

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

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

List contains all the recognized USAN stems.

15. **Red Book Pharmacy's Fundamental Reference**

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

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

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

17. **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.⁴

For the proposed proprietary name, DMEPA Safety Evaluators 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 Safety Evaluators also conduct internal CDER prescription analysis studies. When provided, DMEPA considers external prescription analysis study results and incorporate into the overall risk assessment.

The Safety Evaluator assigned to the Proprietary Name Risk Assessment is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name. DMEPA bases the overall risk assessment on the findings of a Failure Mode and Effects Analysis (FMEA) of the proprietary name, and focuses on the avoidance of medication errors.

FMEA is a systematic tool for evaluating a process and identifying where and how it might fail.⁵ 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 Safety Evaluators 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 Safety Evaluators consider 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 Safety Evaluators consider the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.⁶ DMEPA provides the product characteristics considered for this review in section one.

The Division of Medication Error Prevention and Analysis considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. DMEPA also compares the spelling of the proposed proprietary name with the proprietary and established name of existing and proposed drug products because similarly spelled names may have greater likelihood to sound similar to one another when spoken or look similar to one another when scripted. DMEPA Safety Evaluators also examine the orthographic appearance of the proposed name using a number of different handwriting samples. Handwritten communication of drug names has a long-standing association with drug name confusion. Handwriting can cause similarly and even dissimilarly spelled drug name pairs to appear very similar to one another. The similar appearance of drug names when scripted has led

⁴ National Coordinating Council for Medication Error Reporting and Prevention. <http://www.nccmerp.org/aboutMedErrors.html>. Last accessed 10/11/2007.

⁵ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

⁶ Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

to medication errors. The DMEPA Safety Evaluators apply 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 Safety Evaluators compare the pronunciation of the proposed proprietary name with the pronunciation of other drug names because verbal communication of medication names is common in clinical settings. If provided, DMEPA will consider the Applicant’s intended pronunciation of the proprietary name. However, DMEPA also considers a variety of pronunciations that could occur in the English language because the Applicant has little control over how the name will be spoken in clinical practice.

Table 1. Criteria used to identify drug names that look- or sound-similar to a proposed proprietary name.

Type of similarity	Considerations when searching the databases		
	Potential causes of drug name similarity	Attributes examined to identify similar drug names	Potential Effects
L alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	<ul style="list-style-type: none"> Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communication Names may look similar when scripted and lead to drug name confusion in written communication
	Orthographic similarity	Similar spelling Length of the name Upstrokes Down strokes Cross-strokes Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	<ul style="list-style-type: none"> Names may look similar when scripted, and lead to drug name confusion in written communication
Sound-alike	Phonetic similarity	Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics	<ul style="list-style-type: none"> Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Lastly, the DMEPA Safety Evaluators also consider 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 Safety Evaluators conduct 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 Safety Evaluators 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 Safety Evaluators 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) Safety Evaluators 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 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 or Generic drugs

DMEPA requests the Office of New Drugs (OND) or Office of Generic Drugs (OGD) Regulatory Division responsible for the application for their 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 or 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 concur/not concur with DMEPA's final decision.

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, 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.⁷ When applying FMEA to assess the risk of a proposed proprietary name, DMEPA seeks to evaluate the potential for a proposed proprietary name to be confused with another drug name because of name confusion and, thereby, cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to orthographically or phonetically similar drug names prior to approval, where actions to overcome these issues are easier and more effective than remedies available in the post-approval phase.

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

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

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

An affirmative answer indicates a failure mode and represents a potential for the proposed proprietary name to be confused with another proprietary or established drug name because of look- or sound-alike similarity. If the answer to the question is no, the Safety Evaluator is not convinced that the names possess similarity that would cause confusion at any point in the medication use system, thus the name is eliminated from further review.

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

“Could the confusion of the drug names conceivably result in medication errors in the usual practice setting?”

⁷ Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

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

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

- a. DDMAC finds the proposed proprietary name misleading from a promotional perspective, and the Review Division concurs with DDMAC's findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a PROPRIETARY name or otherwise [21 U.S.C 321(n); See also 21 U.S.C. 352(a) & (n)].
- b. DMEPA identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].
- c. FMEA identifies the potential for confusion between the proposed proprietary name and other proprietary or established drug name(s), and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.
- d. The proposed proprietary name contains an USAN (United States Adopted Names) stem.
- e. DMEPA identifies a potential source of medication error within the proposed proprietary name. For example, the proprietary name may be misleading or, inadvertently, introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug product.

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

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

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

Furthermore, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to rectify post-approval. Educational and other post-approval efforts are low-leverage strategies that have had limited effectiveness at alleviating medication errors involving drug name confusion. Applicants have undertaken higher-leverage strategies, such as drug name changes, in the past but at great financial cost to the Applicant and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for approving the error-prone proprietary name. Moreover, even after Applicants' have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioners' vocabulary, and as a result, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, DMEPA believes that post-approval efforts at reducing name confusion errors should be reserved for those cases in which the potential for name confusion could not be predicted prior to approval. (See Section 4 for limitations of the process).

Appendix B: Letters with possible orthographic or phonetic misinterpretation

Letters in proposed name "Erwinaze"	When scripted may appear as:	When spoken may be interpreted as:
Capital 'E'	Capital 'F', 'C'	Any vowel
Lower case 'r'	'n', 's', 'v', 'u', 'x', or 't'	
Lower case 'w'	'v', 'u', or 'm'	'v'
Lower case 'i'	'e' or 'l'	Any vowel
Lower case 'n'	'm', 'u', 'x', 'r', 'h', or 's'	
Lower case 'a'	'c', 'o', or 'u'	Any vowel
Lower case 'z'	'c', 'l', 'm', 'n', 'r', 's', 't', and 'x'	's'
Lower case 'e'	'i', 'l', or 'o'	Any vowel
'Er'		'Ir' or 'Ur'
'win'		'when' or 'wen'

Appendix C: FDA Prescription Study Responses

Inpatient Medication Order	Outpatient Medication Order	Voice Prescription
Ervinage	Ervinase	???
Ervinaze	Erurnare	Erenase
Ervinaze	Erwinare	Erwinase
Ervinaze	Erwinare	Erwinase
Ervinaze	Fruinare	Erwinase
Ervinaze	Furnase	Erwinease
Eriwinaze	Zruvinare	Erwinese
Eruvinaze	Zruinase	Irinase
Erwinase	Zrurinare	Irwinase
Erwinaze	Zrurinase	Irwinaze
Erwinaze	Zrurnare	Irwinese
Erwinaze	Zruvinare	irwinez
Erwinaze	Zurnare	Oenesis
Erwingazi	Zuvinare	Urwinase

Appendix D: Names Lacking Orthographic and/or Phonetic Similarity

Name	Similarity to Erwinaze
Unicare	Look
Enoxacin	Look
Ertaczo	Look
Arranon	Look
Etretinate	Look
Amphadase	Look
Arimidex	Look
Arixtra	Look
Avage	Look
Eurax	Look
Retavase	Look
Wydase	Look
Aranesp	Sound
Errin	Look
Iressa	Look
Cervarix	Look
Eraxis	Look

Appendix E: Products that are not currently marketed in the U.S.

Proprietary Name	Similarity to Erwinaze	Description	Status
Renese	Look	Renese (polythiazide) tablets: 1 mg, 2 mg, 4 mg Renese-R (polythiazide and reserpine) tablets: 2 mg/0.25 mg	Brand name products discontinued; generics not available (b) (4)
Urese (Benzthiazide)	Look	Tablets: 25 mg	Brand name product discontinued; generics not available (b) (4)

Appendix F: Name that has never been marketed in the U.S.

Proprietary Name	Similarity to Erwinaze	Description	Disposition
(b) (4)			

Appendix G: Proprietary or Established Names used only in Foreign Countries

Proprietary Name	Similarity to Erwinaze	Country	Comments
Brevinaze (Ketamine Hydrochloride)	Look	South Africa	This product has been discontinued

Appendix H: Products with no overlap in strength or dose

Erwinaze (Erwinia L-asparaginase) for Injection		Powder for injection: 10,000 International Units per vial	25,000 International Units/m ² via intramuscular injection three times a week for two weeks for every course of asparaginase treatment
Product name with potential for confusion	Similarity to Erwinaze	Strength	Usual Dose (if applicable)
Micronase (Glyburide) *Brand name product discontinued; generics available	Look	Tablets: 1.25 mg, 2.5 mg, 5 mg	The usual starting dose of Micronase tablets is 2.5 mg to 5 mg orally once daily, administered with breakfast or the first main meal. Those patients who may be more sensitive to hypoglycemic drugs should be started at 1.25 mg daily. The usual maintenance dose is in the range of 1.25 mg to 20 mg daily, which may be given as a single dose or in two divided doses.
Invirase (Saquinavir)	Look	Capsule: 200 mg Tablet: 500 mg	Adults (Over the Age of 16 Years): Invirase 1000 mg orally twice daily (5 x 200 mg capsules or 2 x 500 mg tablets) in combination with ritonavir 100 mg orally twice daily. Ritonavir should be taken at the same time as Invirase. Invirase and ritonavir should be taken within 2 hours after a meal.
Amerge (Naratriptan HCl)	Look	Tablets: 1 mg and 2.5 mg	1 mg or 2.5 mg once, may repeat dose after 4 hours if needed
Buminate (Human Albumin)	Look	Injection: 5% and 25%	Individualize the dose 5%: 250 mL to 500 mL intravenously over 30 minutes 25%: 100 mL to 200 mL intravenously over 30 minutes
FreAmine Line of amino acid injections and amino acid/electrolyte injections used for parenteral nutrition. Partial listing: FreAmine HBC 6.9% FreAmine III 10% FreAmine III 8.5% FreAmine III 3%	Look	Varies per product. See product listing in the left column.	These products are typically used as a source of amino acids in the preparation of parenteral nutrition in a pharmacy setting. These products are not typically dispensed for direct patient administration.

Erwinaze (Erwinia L-asparaginase) for Injection		Powder for injection: 10,000 International Units per vial	25,000 International Units/m² via intramuscular injection three times a week for two weeks for every course of asparaginase treatment
Product name with potential for confusion	Similarity to Erwinaze	Strength	Usual Dose (if applicable)
Carnosine	Look	Dietary supplement	500 mg, one, two, or three times per day
Orabase Line of dental products (partial listing): Orabase B: benzocaine oral paste; 20% (nonprescription) Orabase Plain: plasticized hydrocarbon gel oral paste (nonprescription) Orabase HCA: hydrocortisone acetate oral paste; 0.5% (prescription)	Look	Varies per product. See product listing in the left column.	These products are applied topically to the affected area. Can be used up to four times per day.
(b) (4)			

⁸Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at (www.thomsonthomson.com).
Accessed on August 30, 2010.

Appendix I: Products with Multiple Differentiating Product Characteristics

Erwinaze (Erwinia L-asparaginase) for Injection	Similarity to Erwinaze	Strength	Usual Dose	Other Differentiating Product Characteristics (Product vs. Erwinaze)
Erwinaze (Erwinia L-asparaginase)		Powder for injection: 10,000 International Units per vial	25,000 International Units/m ² via intramuscular injection three times a week for two weeks for every course of asparaginase treatment	
OraVerse (Phentolamine Mesylate)	Look	Injection: 0.4 mg/1.7 mL solution per cartridge	The recommended dose of OraVerse is based on the number of cartridges of local anesthetic with vasoconstrictor administered: 0.2 mg (1/2 cartridge), 0.4 mg (1 cartridge), or 0.8 mg (2 cartridges)	Route of administration: Intramuscular injection vs. infiltration or block injection Dose: 25,000 International Units/m ² vs. dependent on amount of local anesthetic administered Frequency of administration: Three times a week for two weeks for every course of asparaginase treatment vs. once, following the dental procedure
Beconase AQ (Beclomethasone Dipropionate Monohydrate) 42 mcg/inhalation Beconase (Beclomethasone Dipropionate) 42 mcg/inhalation <i>(This product has been discontinued and there are no generics available)</i>	Look	Nasal spray: 42 mcg per inhalation	The usual dosage is 1 or 2 nasal inhalations (42 mcg to 84 mcg) in each nostril twice a day (total dose, 168 to 336 mcg/day).	Dosage Form: Powder for injection vs. nasal spray Route of administration: Intramuscular injection vs. intranasal Dose: 25,000 International Units/m ² vs. 1 or 2 nasal inhalations (42 to 84 mcg) in each nostril Frequency of administration: Three times a week for two weeks for every course of asparaginase treatment vs. twice a day

Erwinaze (<i>Erwinia L</i> -asparaginase) Injection	Similarity to Erwinaze	Strength	Usual Dose	Other Differentiating Product Characteristics (Product vs. Erwinaze)
Erwinaze (<i>Erwinia L</i> -asparaginase)		Powder for injection: 10,000 International Units per vial	25,000 International Units/m ² via intramuscular injection three times a week for two weeks for every course of asparaginase treatment	
CaviRinse (Sodium Fluoride)	Look	Oral solution: 0.2%	10 mL rinse or apply to teeth daily and spit after brushing	<p><u>Dosage Form:</u> Powder for injection vs. oral solution</p> <p><u>Route of administration:</u> Intramuscular injection vs. oral rinse</p> <p><u>Dose:</u> 25,000 International Units/m² vs. 10 mL</p> <p><u>Frequency of administration:</u> Three times a week for two weeks for every course of asparaginase treatment vs. once weekly</p>
Orinase (tolbutamide) Tablets Orinase Diagnostic (Tolbutamide Sodium) Injection	Look and Sound	<p>Tablets: 250 mg, 500 mg</p> <p>*Brand name product discontinued; generics available only in the 500 mg strength</p> <p>Injection: 1 gram per vial</p> <p>*Brand name product discontinued; generics not available</p>	Initially, 1000 mg to 2000 mg per day orally given in 1 to 3 divided doses. The usual dosage range is 250 mg to 2000 mg per day. Maximum dosage is 3000 mg per day.	<p><u>Dosage Form:</u> Powder for injection vs. oral tablets</p> <p><u>Route of administration:</u> Intramuscular injection vs. oral</p> <p><u>Dose:</u> 25,000 International Units/m² vs. 1000 mg to 2000 mg per day</p> <p><u>Frequency of administration:</u> Three times a week for two weeks for every course of asparaginase treatment vs. given in 1 to 3 divided doses</p>

Erwinaze (<i>Erwinia</i> L-asparaginase) Injection	Similarity to Erwinaze	Strength	Usual Dose	Other Differentiating Product Characteristics (Product vs. Erwinaze)
Erwinaze (<i>Erwinia</i> L-asparaginase)		Powder for injection: 10,000 International Units per vial	25,000 International Units/m ² via intramuscular injection three times a week for two weeks for every course of asparaginase treatment.	
Evamist (Estradiol)	Look	Transdermal spray: 1.53 mg/spray	One spray once daily to forearm as a starting dose. Increase to two or three sprays daily to forearm based upon clinical response.	<p><u>Dosage Form:</u> Powder for injection vs. transdermal spray</p> <p><u>Route of administration:</u> Intramuscular injection vs. topically to forearm</p> <p><u>Dose:</u> 25,000 International Units/m² vs. one, two, or three sprays</p> <p><u>Frequency of administration:</u> Three times a week for two weeks for every course of asparaginase treatment vs. once daily</p>
Aromasin (Exemestane)	Look	Tablets: 25 mg	The recommended dose in early and advanced breast cancer is 25 mg (1 tablet) once daily after a meal.	<p><u>Dosage Form:</u> Powder for injection vs. oral tablets</p> <p><u>Route of administration:</u> Intramuscular injection vs. oral</p> <p><u>Dose:</u> 25,000 International Units/m² vs. 25 mg (1 tablet)</p> <p><u>Frequency of administration:</u> Three times a week for two weeks for every course of asparaginase treatment vs. once daily after a meal</p>

Erwinaze (<i>Erwinia L-asparaginase</i>) Injection	Similarity to Erwinaze	Strength	Usual Dose	Other Differentiating Product Characteristics (Product vs. Erwinaze)
Erwinaze (<i>Erwinia L-asparaginase</i>)		Powder for injection: 10,000 International Units per vial	25,000 International Units/m ² via intramuscular injection three times a week for two weeks for every course of asparaginase treatment	
Enulose (Lactulose)	Look	Solution (oral/rectal): 10 grams/15 mL	<p>Treatment of hepatic encephalopathy: Oral dose: Initially, 30 to 45 mL (20 to 30 grams lactulose) orally given 3 to 4 times per day. If necessary, hourly doses of 30 to 45 mL orally may be given until a laxative effect is induced. Once a laxative effect has been established, dosage should be reduced to produce 2 to 3 loose stools daily.</p> <p>Rectal dose: Initially, 300 mL lactulose, diluted with 700 mL water or normal saline, and administered via rectal balloon catheter and retained for 30 to 60 minutes. May repeat every 4 to 6 hours as needed.</p> <p>Treatment of constipation: Initially, 15 to 30 mL orally once daily, increasing to 60 mL orally once daily if needed.</p>	<p>Dosage Form: Powder for injection vs. solution</p> <p>Route of administration: Intramuscular injection vs. oral or rectal</p> <p>Dose: 25,000 International Units/m² vs. 15 to 60 mL orally or 300 mL rectally</p> <p>Frequency of administration: Three times a week for two weeks for every course of asparaginase treatment vs. once daily, 3 to 4 times per day, hourly, or every 4 to 6 hours</p>

Erwinaze (<i>Erwinia</i> L-asparaginase) Powder for Injection	Similarity to Erwinaze	Strength	Usual Dose	Other Differentiating Product Characteristics (Product vs. Erwinaze)
Erwinaze (<i>Erwinia</i> L-asparaginase)		Powder for injection: 10,000 International Units per vial	25,000 International Units/m ² via intramuscular injection three times a week for two weeks for every course of asparaginase treatment	
AllerNaze (Triamcinolone Acetonide)	Look	Nasal Spray: 50 mcg per spray	Two or four sprays in each nostril once daily; two sprays in each nostril twice daily	<p><u>Dosage Form:</u> Powder for injection vs. nasal spray</p> <p><u>Route of administration:</u> Intramuscular injection vs. nasal spray</p> <p><u>Dose:</u> 25,000 International Units/m² vs. 200 mcg or 400 mcg</p> <p><u>Frequency of administration:</u> Three times a week for two weeks for every course of asparaginase treatment vs. once daily or twice daily</p>

Appendix J: Product with strong orthographic similarity but different product characteristics

Failure Mode: Name confusion	Causes (could be multiple)	Effects
<p>Erwinaze (<i>Erwinia</i> L-asparaginase)</p>	<p>Powder for injection: 10,000 IU per vial</p>	<p>25,000 International Units/m² via intramuscular injection three times a week for two weeks for every course of asparaginase treatment</p>
<p>Eminase (Anistreplase) powder for injection</p> <p><i>Strength:</i> 30 units per vial</p> <p><i>Dosage:</i> The recommended dose is 30 units administered by intravenous injection over 2 to 5 minutes into an intravenous line or vein</p>	<p>Orthographic similarities: Both names begin with the letter "E". The letter "m" may look similar to the letters "rw". Additionally, the letters "inase" are identical to both names.</p> <p>Phonetic similarities: Both names contain three syllables. The second and third syllables in the names ("min-ase" vs. "win-ase") sound similar.</p> <p>Single strength</p> <p>Overlapping measure (units)</p>	<p>The risk of medication errors in the usual practice setting will be reduced by the differences in the product characteristics.</p> <p><i>Rationale:</i></p> <p>The recommended dose of Eminase is 30 units via intravenous injection as a one time dose. By contrast, the recommended dose of Erwinaze is 25,000 International Units/m² via intramuscular injection three times a week for two weeks for every course of asparaginase treatment.</p> <p>Further, Eminase does not appear to be marketed in the U.S. We were unable to identify this product in Drugs@FDA, Orange Book, Red Book, Facts and Comparisons, Lexicomp, CVS, RxList, or Walgreens. The USPTO lists two dead trademarks for fibrinolytic agents, registered to SmithKline Beecham or Beecham Incorporated. SAEGIS lists two U.S. Federal trademarks, one expired and one cancelled, in addition to trademarks in several foreign countries, most of which are expired. Additionally, per SAEGIS the year of last recorded sales was 2000⁹. We identified two IND's in DARRTS under the established name, anistreplase. These IND's have been either withdrawn or terminated. Clinical Pharmacology lists dosing recommendations and indicates that anistreplase was approved by the FDA in June 1990, but we cannot find any FDA information to support this. Micromedex indicates that Eminase is available through GlaxoSmithKline, but the product is not listed on the company's website. Micromedex also indicates that the product has been discontinued by Roberts, USA, but we were unable to find a website for this company. We found product information via a Google search. (b) (4)</p> <p>(b) (4)</p>

⁹Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at (www.thomsonthomson.com). Accessed on September 6, 2010.

Failure Mode: Name confusion	Causes (could be multiple)	Effects
Erwinaze (Erwinia L-asparaginase)	Powder for injection: 10,000 IU per vial	25,000 International Units/m² via intramuscular injection three times a week for two weeks for every course of asparaginase treatment
Urokinase for Injection <i>Strength:</i> 250,000 International Units per vial <i>Dosage:</i> For the treatment of massive acute pulmonary embolism or pulmonary embolism associated with hemodynamic instability: 4400 International Units/kg via intravenous infusion over 10 minutes, followed by continuous intravenous infusion of 1400 International Units/kg/hr for 12 hours. Administration may be repeated as needed.	<p>Orthographic similarities: Both names contain the letter "r" in the second position and the identical sequential letters "ina". Both names end with the letter "e". The letters "z" in Erwinaze may look similar to the letter "s" in Urokinase when scripted without a downstroke.</p> <p>Both products have the dosage designation "units" in the strength. A dose of Urokinase is achievable using Erwinaze and vice versa.</p>	<p>The risk of medication errors in the usual practice setting will be reduced by orthographic differences between the names.</p> <p><i>Rationale:</i></p> <p>The beginning letters of the names ("E" vs. "U") look different when scripted. Additionally, the letter "w" in Erwinaze does not look similar to the letters "ok" in Urokinase which may help to differentiate the names.</p> <p>The context of use for the products is different. Urokinase is indicated for the treatment of massive acute pulmonary embolism and the treatment of deep vein thrombosis and other thrombotic/embolic states whereas Erwinaze is a chemotherapeutic agent indicated for the treatment of acute lymphoblastic leukemia. Additionally, the route of administration (intramuscular vs. intravenous) differs between the products.</p>